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(54) Title: METHODS OF TREATING INFLAMMATION OR NEUROPATHIC PAIN

(57) Abstract: Provided herein are methods of treating inflammation or neuropathic pain using an effective dose of a monoacylglycerol lipase inhibitor or a composition thereof.

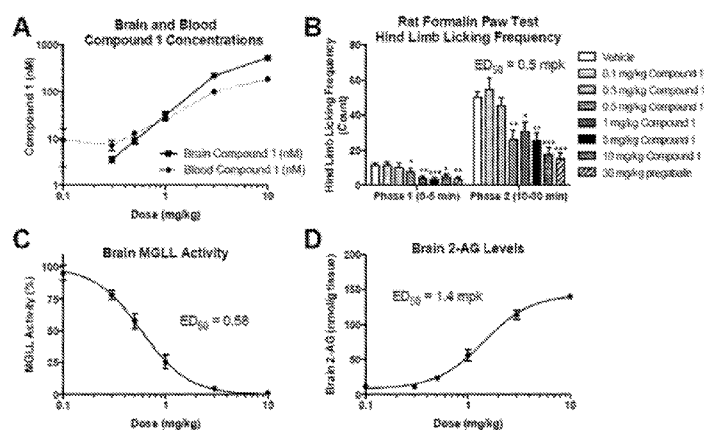


Fig. 3



TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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METHODS OF TREATING INFLAMMATION OR NEUROPATHIC PAIN

CROSS-REFERENCE

[0001] The present application claims the benefit of U.S. Provisional Application No. 62/159,770, filed May 11, 2015, and U.S. Provisional Application No. 62/297,670, filed February 19, 2016, both of which are incorporated herein by reference in their entireties.

BACKGROUND

[0002] Monoacylglycerol lipase (MGLL or MAGL) is an enzyme responsible for hydrolyzing endocannabinoids such as 2-AG (2-arachidonoylglycerol), an arachidonate based lipid, in the nervous system.

SUMMARY OF THE INVENTION

[0003] Disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 500 mg.

[0004] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the concentration of plasma 2-AG of the patient increases at least 2-fold after administration of the effective dose.

[0005] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein a fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from the patient after administration of the effective dose.

[0006] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.05 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. Further disclosed herein are methods of treating inflammation or neuropathic pain in

a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.1 \mu M \cdot hr$ after administration of the effective dose. Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.2 \mu M \cdot hr$ after administration of the effective dose.

[0007] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.05 \mu M \cdot hr$ after administration of the effective dose. Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.1 \mu M \cdot hr$ after administration of the effective dose. Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.2 \mu M \cdot hr$ after administration of the effective dose.

[0008] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein after administration of the effective dose: (a) the concentration of plasma 2-AG of the patient increases at least 2-fold; and (b) a fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from the patient.

[0009] Disclosed herein is also 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1) or a pharmaceutically acceptable salt thereof, for use as a medicament. Further disclosed herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in a method of treating inflammation, pain, or neuropathic pain of the human or animal body; wherein the effective dose is from about 1 mg to about 500 mg; or wherein the concentration of plasma 2-AG of the patient increases at least 2-fold after administration of the effective dose; or wherein a

fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from the patient after administration of the effective dose; or wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.05 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose; or wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.1 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose; or wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.2 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose; or wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.05 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose; or wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.1 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose; or wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.2 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose; or wherein after administration of the effective dose: (a) the concentration of plasma 2-AG of the patient increases at least 2-fold; and (b) a fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from the patient.

[0010] Further disclosed herein are methods of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg.

[0011] Further disclosed herein are methods of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg.

[0012] Further disclosed herein is also Compound 1 or a pharmaceutically acceptable salt thereof, for use in a method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, abdominal pain associated with Irritable Bowel Syndrome, acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis,

functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein the effective dose is from about 1 mg to about 100 mg.

[0013] In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 3-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 4-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 5-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 6-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 7-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 8-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 9-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient increases at least 10-fold after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the concentration of plasma 2-AG of the patient is measured in an *in vitro* assay.

[0014] In some embodiments of the methods and medical uses described herein, a fragment of Compound 1 is covalently attached to at least 40% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments of the methods and medical uses described herein, a fragment of Compound 1 is covalently attached to at least 50% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments of the methods and medical uses described herein, a fragment of Compound 1 is covalently attached to at least 60% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments of the methods and medical uses described herein, a fragment of Compound 1 is covalently attached to at least 70% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments of the methods and medical uses described herein, a fragment of Compound 1 is covalently attached to at least 80% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments of the methods and medical uses

described herein, a fragment of Compound 1 is covalently attached to at least 90% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments of the methods and medical uses described herein, measurement of fragments of Compound 1 covalently attached to MGLL in PBMCs from the patient is performed using an *in vitro* assay.

[0015] In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 0.3 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 0.4 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 0.5 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 0.6 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 0.7 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 0.8 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 0.9 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the plasma AUC_{0-inf} of Compound 1 is at least 1.0 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.

[0016] In some embodiments of the methods and medical uses described herein, the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.3 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.4 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.5 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.6 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.7 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.8 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the

steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.9 \mu\text{M}\cdot\text{hr}$ after administration of the effective dose. In some embodiments of the methods and medical uses described herein, the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least $1.0 \mu\text{M}\cdot\text{hr}$ after administration of the effective dose.

[0017] In some embodiments of the methods and medical uses described herein, the effective dose is from about 1 mg to about 500 mg. In some embodiments of the methods and medical uses described herein, the effective dose is from about 2 mg to about 400 mg. In some embodiments of the methods and medical uses described herein, the effective dose is from about 10 mg to about 160 mg. In some embodiments of the methods and medical uses described herein, the effective dose is from about 2 mg to about 100 mg. In some embodiments of the methods and medical uses described herein, the effective dose is from about 2 mg to about 50 mg. In some embodiments of the methods and medical uses described herein, the effective dose is from about 2 mg to about 20 mg.

[0018] In some embodiments of the methods and medical uses described herein, Compound 1 is administered orally. In some embodiments of the methods and medical uses described herein, the effective dose is taken with food. In some embodiments of the methods and medical uses described herein, the effective dose is taken without food. In some embodiments of the methods and medical uses described herein, the effective dose is administered to the patient once per day. In some embodiments of the methods and medical uses described herein, the effective dose is administered to the patient twice per day. In some embodiments of the methods and medical uses described herein, the effective dose is administered to the patient three times per day.

[0019] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma $AUC_{0-\infty}$ of at least $0.05 \mu\text{M}\cdot\text{hr}$. **Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma $AUC_{0-\infty}$ of at least $0.1 \mu\text{M}\cdot\text{hr}$.** Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma $AUC_{0-\infty}$ of at least $0.2 \mu\text{M}\cdot\text{hr}$.

[0020] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition increases the concentration of plasma 2-AG in the patient by at least 2-fold.

[0021] Further disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.

[0022] Further disclosed herein is also a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating inflammation or neuropathic pain of the human or animal body; wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.05 \mu M \cdot hr$; or wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.1 \mu M \cdot hr$; or wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.2 \mu M \cdot hr$; or wherein administration of the composition increases the concentration of plasma 2-AG in the patient by at least 2-fold; or wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.

[0023] Further disclosed herein are methods of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.05 \mu M \cdot hr$. Further disclosed herein are methods of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.1 \mu M \cdot hr$. Further disclosed herein are methods of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising

Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.2 \mu M \cdot hr$.

[0024] Further disclosed herein are methods of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.05 \mu M \cdot hr$. **Further disclosed herein are methods of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.1 \mu M \cdot hr$. Further disclosed herein are methods of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.2 \mu M \cdot hr$.**

[0025] Further disclosed herein is also a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, abdominal pain associated with Irritable Bowel Syndrome, acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia; wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.05 \mu M \cdot hr$. **Further disclosed herein is also a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method**

of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, abdominal pain associated with Irritable Bowel Syndrome, acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia; wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.1 \mu M \cdot hr$. Further disclosed herein is also a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, abdominal pain associated with Irritable Bowel Syndrome, acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia; wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.2 \mu M \cdot hr$.

[0026] Further disclosed herein are methods of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.

[0027] Further disclosed herein are methods of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.

[0028] Further disclosed herein is also thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, abdominal pain associated with Irritable Bowel Syndrome,

acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia; wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.

[0029] Further disclosed herein are methods and medical uses of increasing the concentration of plasma 2-AG in a subject using an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the concentration of plasma 2-AG in a subject is increased by at least 2-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 3-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 4-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 5-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 6-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 7-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 8-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 9-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 10-fold.

[0030] Further disclosed herein are methods of binding MGLL with Compound 1 in PBMCs in a subject after administration of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject, wherein a fragment of Compound 1 is covalently attached to at least 30% MGLL in PBMCs. Further disclosed herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in any one of the methods of therapy disclosed herein, wherein after administration of an effective dose of Compound 1, a fragment of Compound 1 is covalently attached to at least 30% MGLL in PBMCs of a subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 40% of MGLL in PBMCs from the subject after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 50% of MGLL in PBMCs from the subject after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 60% of MGLL in PBMCs from the subject after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 70% of MGLL in PBMCs from the subject after administration of the effective dose. In some embodiments, a

fragment of Compound 1 is covalently attached to at least 80% of MGLL in PBMCs from the subject after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 90% of MGLL in PBMCs from the subject after administration of the effective dose. In some embodiments, the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, Compound 1 is administered orally.

[0031] Further disclosed herein are pharmaceutical compositions comprising an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. Further disclosed herein are pharmaceutical compositions for the treatment of inflammation or neuropathic pain, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. Further disclosed herein are pharmaceutical compositions for use in a method of treatment of inflammation or neuropathic pain of the human or animal body, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[0032] Further disclosed herein are pharmaceutical compositions for the treatment of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. Further disclosed herein are pharmaceutical compositions for use in a method of treatment

of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[0033] Further disclosed herein are pharmaceutical compositions for the treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. Further disclosed herein are pharmaceutical compositions for use in a method of treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] The novel features of the invention are set forth with particularity in the appended claims. The invention is best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that,

according to common practice, the various features of the drawings are not to-scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

[0035] **FIG. 1** shows the MGLL target engagement in the rhesus brain as a function of Compound 1 administered dose (IV administration).

[0036] **FIG. 2A-D** show the time course effects following a single dose of Compound 1 in rats. Single dose Compound 1 (3 mg/kg, PO, $n=3$) induced time-dependent effects on MGLL activity (A), brain 2-AG concentrations (B), and Compound 1 concentrations (C). After Compound 1 concentrations fell below detection, MGLL activity recovered at an average rate of approximately 2%/h (D). Results shown for one representative experiment. Data are presented as mean $\pm$ standard error of the mean (SEM).

[0037] **FIG. 3A-D** show antinociceptive effects of single dose Compound 1 in the rat formalin paw test. Following single-dose Compound 1 administration (0.1-10 mg/kg, PO, 4-4.75 hours, $n=10$), Compound 1 concentrations (A) are associated with reduced nociceptive paw licking behavior (B), brain MGLL activity (C), and elevated brain 2-AG concentrations (D). Results for one representative experiment are shown. Data are presented as the mean $\pm$ standard error of the mean (SEM). * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ significantly different from vehicle by Dunnett's post hoc tests following one-way analysis of variance (ANOVA).

[0038] **FIG. 4A-B** shows inhibition of MGLL activity in rat PBMC and elevation of rat plasma 2-AG concentrations by Compound 1. (A) Single-dose administration of Compound 1 (0.03-30 mg/kg, PO, 4 h, $n=3$ rats per dose) inhibited MGLL activity in rat PBMC with an ED_{50} of 0.07 mg/kg. MGLL activity was observed in rat PBMC by ABPP with the fluorophosphonate-rhodamine activity probe and the ED_{50} value was calculated by non-linear regression of log-transformed data. (B) Single-dose administration of Compound 1 (0.1-10 mg/kg, PO, 4 h, $n=2$ rats per dose) elevated plasma 2-AG concentrations by up to 7-fold. Plotted data represent the mean $\pm$ standard error of the mean (SEM).

[0039] **FIG. 5A-B** shows inhibition of MGLL activity in human PBMC by Compound 1. (A) MGLL activity was observed in human PBMC by activity-based protein profiling (ABPP) with the fluorophosphonate-rhodamine activity probe. Treatment with Compound 1 (10 μ M, 30 min, 37°C) inhibited MGLL activity in human PBMC. Partial inhibition of carboxylesterase 1 (CES1) was also observed. (B) MGLL activity was measured by 2-AG hydrolysis in PBMC lysates isolated from human whole blood from two human donors 5569 and 5392 treated with Compound 1 (0.3-1000 nM, 30 min, 37°C, $n=2$ replicates per

concentration per donor). MGLL activity was completely inhibited by 1 μ M of Compound 1 with an average IC_{50} value of 47 ± 5 nM (mean $\pm$ standard deviation). Plotted data represent the mean $\pm$ standard deviation.

[0040] FIG. 6 shows the time and dose dependent inhibition of MGLL activity following oral administration of Compound 1 to human subjects using exogenous 2-AG as a substrate to assay *ex vivo* MGLL-mediated hydrolysis in PBMC.

[0041] FIG. 7 shows mean Compound 1 plasma concentrations measured on Days 1 and 13 in Panel C (10 mg QD x 14 days).

[0042] FIG. 8 shows mean Compound 1 plasma concentrations measured on Days 1 and 13 in Panel D (20 mg QD x 14 days).

[0043] FIG. 9 shows mean percent of Day 1 pre-dose baseline PBMC-mediated hydrolysis of 2-AG versus time post-dose in Placebo recipients (Panels C and D combined).

[0044] FIG. 10 shows mean percent of Day 1 pre-dose baseline PBMC-mediated hydrolysis of 2-AG versus time post-dose in Panel C (10 mg QD x 14 days).

[0045] FIG. 11 shows mean percent of Day 1 pre-dose baseline PBMC-mediated hydrolysis of 2-AG versus time post-dose in Panel D (20 mg QD x 14 days).

DETAILED DESCRIPTION OF THE INVENTION

[0046] MGLL is an enzyme that catalyzes the hydrolysis of the endocannabinoid 2-arachidonoylglycerol (2-AG), an endogenous ligand of the cannabinoid receptors CB_1 and CB_2 , which are the molecular targets of the psychoactive component of *Cannabis sativa*, Δ^9 -tetrahydrocannabinol (THC). In rodents, MGLL is the major 2-AG hydrolase in the CNS as well as in most peripheral tissues and is the primary enzyme controlling the levels of 2-AG available to signal through $CB_{1,2}$.

[0047] CB_1 is the primary cannabinoid receptor in the nervous system and is widely distributed throughout the brain and at lower levels in peripheral tissues. Activation of CB_1 accounts for most of the neurobehavioral effects of THC and other exogenous cannabinoids (exocannabinoids) in rodents and humans. CB_2 is expressed primarily on immune cells and mediates the immunosuppressive effects of exocannabinoids. Direct activation of cannabinoid receptors by *Cannabis* preparations (e.g., Sativex[®]), THC (e.g., Marinol[®]), and cannabinoid agonists (e.g., Cesamet[®]) elicits therapeutically beneficial effects on pain, spasticity, sleep, appetite, and nausea.

[0048] The product of 2-AG hydrolysis, AA, is the metabolic precursor for the prostanoid family of signaling lipids. MGLL contributes to AA and prostanoid production in the rodent nervous system and select peripheral tissues, including the liver and lung.

Genetic or pharmacologic inactivation of MGLL in mice reduces neuroinflammation in models of neurodegeneration through mechanisms independent of cannabinoid receptors, suggesting involvement of prostanoid suppression (Nomura, Science, 2011; Chen, Cell Reports, 2012; Piro, Cell Reports, 2012).

[0049] This disclosure is directed, at least in part, to methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administration to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof. Further disclosed herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in a method of treating inflammation or neuropathic pain of the human or animal body. In another aspect, disclosed herein are methods of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administration to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof. Further disclosed herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in a method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome. In another aspect, disclosed herein are methods and medical uses to increase the concentration of plasma 2-arachidonoylglycerol (2-AG) in a subject at least 2- to 10-fold after administration to the subject an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In another aspect, disclosed herein are methods and medical uses to bind at least 50% of MGLL in PBMCs in a subject using an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the methods and medical uses disclosed herein require an effective dose of Compound 1 ranging from about 1 mg to about 500 mg. In some embodiments, the methods and medical uses disclosed herein require an effective dose of Compound 1 ranging from about 1 mg to about 100 mg. In some embodiments, the methods and medical uses disclosed herein require an effective dose of Compound 1 ranging from about 2 mg to about 20 mg. In some embodiments, the methods and medical uses disclosed herein require a composition comprising Compound 1 which provides a plasma $AUC_{0-\infty}$ of about 0.2 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$ in a subject after administration of Compound 1 to the subject.

[0050] Definitions

[0051] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0052] The singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range varies between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that which in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, use, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

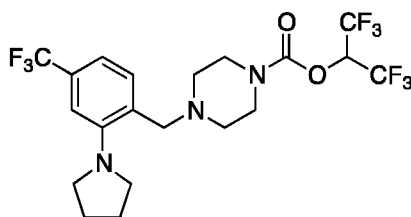
[0053] "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical is or is not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0054] As used herein, "treatment" or "treating" or "palliating" or "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the underlying disorder. For prophylactic benefit, the compositions are administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

[0055] In some embodiments, “subject” and “patient” are used interchangeably. In some embodiments, “subject” refers to a healthy individual. In other embodiments, “subject” refers to a patient in need of treatment. In some embodiments, “subject” refers to a human or an animal, particularly a mammal. In some embodiments, “subject” refers to a human. In some embodiments, “subject” refers to a non-human mammal.

[0056] A “subject group” has a sufficient number of subjects to provide a statistically significant average measurement of a relevant pharmacokinetic parameter.

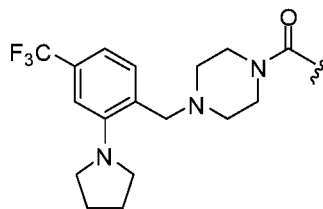
[0057] 1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1) is an irreversible inhibitor of MGLL. Alternate names include, but are not limited to, the following: 1-piperazinecarboxylic acid, 4-[[2-(1-pyrrolidinyl)-4-(trifluoromethyl)phenyl]methyl]-,2,2,2-trifluoro-1-(trifluoromethyl)ethyl ester; 1,1,1,3,3,3-hexafluoropropan-2-yl 4-{[2-(pyrrolidin-1-yl)-4-(trifluoromethyl)phenyl]methyl}piperazine-1-carboxylate; and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl 4-{[2-(1-pyrrolidinyl)-4-(trifluoromethyl)phenyl]methyl}-1-piperazinecarboxylate. Compound 1 has the structure represented by:



[0058] The preparation of Compound 1 was disclosed in WO 2013/103973, the content of which is incorporated by reference in its entirety.

[0059] In some embodiments, a pharmaceutically acceptable salt of Compound 1 is a hydrochloride salt. In further embodiments, the pharmaceutically acceptable salt of Compound 1 is a mono-hydrochloride salt.

[0060] In some embodiments, a fragment of Compound 1 is covalently attached to



MGLL. In some embodiments, the fragment is:

[0061] Methods

Neuropathic Pain and Inflammation

[0062] MGLL inhibitors are efficacious in several rodent models of pain including models of neuropathic pain (Kinsey, JPET, 2009). MGLL inhibitors also reduce disease

and inflammation in multiple preclinical models. In the mouse experimental autoimmune encephalomyelitis model of multiple sclerosis, MGLL inhibition reduced disease severity, prevented demyelination and reduced inflammation (Bernal-Chico, Glia, 2015).

[0063] Disclosed herein are methods of treating pain or inflammation in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the method of treatment is for pain. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the effective dose is administered orally.

[0064] Disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the effective dose is administered orally.

[0065] Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose Compound 1, or a pharmaceutically acceptable salt thereof, wherein the concentration of plasma 2-AG of the patient increases at least 2-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 3-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 4-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 5-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 6-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-

AG of the patient increases at least 7-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 8-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 9-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 10-fold after administration of the effective dose. In some embodiments, the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is administered orally.

[0066] Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein a fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 40% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 50% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 60% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 70% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 80% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 90% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 95% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160

mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is administered orally.

[0067] Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the plasma AUC_{0-inf} of Compound 1 is at least $0.05 \mu M \cdot hr$ after administration of the effective dose. Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the plasma AUC_{0-inf} of Compound 1 is at least $0.01 \mu M \cdot hr$ after administration of the effective dose. Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the plasma AUC_{0-inf} of Compound 1 is at least $0.1 \mu M \cdot hr$ after administration of the effective dose. Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the plasma AUC_{0-inf} of Compound 1 is at least $0.2 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $0.3 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $0.4 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $0.5 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $0.6 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $0.7 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $0.8 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $0.9 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $1.0 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the plasma AUC_{0-inf} of Compound 1 is at least $1.5 \mu M \cdot hr$ after administration

of the effective dose. In some embodiments, the plasma $AUC_{0-\infty}$ of Compound 1 is at least **2.0 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** In some embodiments, the plasma $AUC_{0-\infty}$ of Compound 1 is at least **2.5 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** In some embodiments, the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is administered orally.

[0068] Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.05 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.01 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.1 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.2 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** In some embodiments, the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.3 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** In some embodiments, the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.4 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** In some embodiments, the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.5 $\mu\text{M}\cdot\text{hr}$ after administration of the effective dose.** In some embodiments, the steady state plasma $AUC_{0-\infty}$ of Compound 1 is at least **0.6 $\mu\text{M}\cdot\text{hr}$ after administration of the**

effective dose. In some embodiments, the steady state plasma AUC_{0-inf} of Compound 1 is at least $0.7 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the steady state plasma AUC_{0-inf} of Compound 1 is at least $0.8 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the steady state plasma AUC_{0-inf} of Compound 1 is at least $0.9 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the steady state plasma AUC_{0-inf} of Compound 1 is at least $1.0 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the steady state plasma AUC_{0-inf} of Compound 1 is at least $1.5 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the steady state plasma AUC_{0-inf} of Compound 1 is at least $2.0 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the steady state plasma AUC_{0-inf} of Compound 1 is at least $2.5 \mu M \cdot hr$ after administration of the effective dose. In some embodiments, the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is administered orally.

[0069] Also disclosed herein are methods treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein after administration of the effective dose: (a) the concentration of plasma 2-AG of the patient increases at least 2-fold; and (b) a fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from the patient. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 3-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 4-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 5-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 6-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 7-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient

increases at least 8-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 9-fold after administration of the effective dose. In some embodiments, the concentration of plasma 2-AG of the patient increases at least 10-fold after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 40% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 50% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 60% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 70% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 80% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 90% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, a fragment of Compound 1 is covalently attached to at least 95% of MGLL in PBMCs from the patient after administration of the effective dose. In some embodiments, the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is administered orally.

[0070] Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the method of treatment is for neuropathic pain. In some embodiments, the method of treatment is for inflammation. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100

mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg. In some embodiments, the effective dose is selected from a group described herein. In some embodiments, the composition is administered orally.

[0071] Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least 0.05 $\mu M \cdot hr$. Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least 0.01 $\mu M \cdot hr$. Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least 0.1 $\mu M \cdot hr$. Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least 0.2 $\mu M \cdot hr$. In some embodiments, administration of the composition provides a plasma AUC_{0-inf} of at least 0.3 $\mu M \cdot hr$, at least 0.4 $\mu M \cdot hr$, at least 0.5 $\mu M \cdot hr$, at least 0.6 $\mu M \cdot hr$, at least 0.7 $\mu M \cdot hr$, at least 0.8 $\mu M \cdot hr$, at least 0.9 $\mu M \cdot hr$, at least 1.0 $\mu M \cdot hr$, at least 1.1 $\mu M \cdot hr$, at least 1.2 $\mu M \cdot hr$, at least 1.3 $\mu M \cdot hr$, at least 1.4 $\mu M \cdot hr$, at least 1.5 $\mu M \cdot hr$, at least 1.6 $\mu M \cdot hr$, at least 1.7 $\mu M \cdot hr$, at least 1.8 $\mu M \cdot hr$, at least 1.9 $\mu M \cdot hr$, at least 2.0 $\mu M \cdot hr$, at least 2.1 $\mu M \cdot hr$, at least 2.2 $\mu M \cdot hr$, at least 2.3 $\mu M \cdot hr$, at least 2.4 $\mu M \cdot hr$, at least 2.5 $\mu M \cdot hr$, at least 2.6 $\mu M \cdot hr$, at least 2.7 $\mu M \cdot hr$, at least 2.8 $\mu M \cdot hr$, at least 2.9 $\mu M \cdot hr$, or at least 3.0 $\mu M \cdot hr$. In some embodiments, the composition comprises from about 1 mg to about 500 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 2 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 10 mg to about 160 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 2 mg to about 20

mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered orally.

[0072] Also described herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition increases the concentration of plasma 2-AG in the patient by at least 2-fold. In some embodiments, administration of the composition increases the concentration of plasma 2-AG in the patient by at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold. In some embodiments, the composition comprises from about 1 mg to about 500 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 2 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 10 mg to about 160 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 2 mg to about 20 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered orally.

[0073] Also disclosed herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1. In some embodiments, administration of the composition provides at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%, of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1. In some embodiments, the composition comprises from about 1 mg to about 500 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 2 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 10 mg to about 160 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition comprises from about 2 mg to about 20 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition is administered orally.

[0074] Also described herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a

composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition (a) increases the concentration of plasma 2-AG in the patient by at least 2-fold and (b) provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.

[0075] Also described herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition (a) provides a plasma AUC_{0-inf} of at least $0.05 \mu M \cdot hr$; (b) increases the concentration of plasma 2-AG in the patient by at least 2-fold; and (c) provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1. Also described herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition (a) provides a plasma AUC_{0-inf} of at least $0.01 \mu M \cdot hr$; (b) increases the concentration of plasma 2-AG in the patient by at least 2-fold; and (c) provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1. Also described herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition (a) provides a plasma AUC_{0-inf} of at least $0.1 \mu M \cdot hr$; (b) increases the concentration of plasma 2-AG in the patient by at least 2-fold; and (c) provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1. Also described herein are methods of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, wherein administration of the composition (a) provides a plasma AUC_{0-inf} of at least $0.2 \mu M \cdot hr$; (b) increases the concentration of plasma 2-AG in the patient by at least 2-fold; and (c) provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.

Acute Pain, Inflammatory Pain, Cancer Pain, and Pain Caused by Peripheral Neuropathy

[0076] MGLL inhibitors have shown efficacy in several rodent models of pain including models of acute pain (Long, Nature Chemical Biology, 2009), inflammatory pain (Anderson, Neuropharmacology, 2013), cancer pain (Khasabova, Pharmacology Research,

2011), and pain caused by chemotherapy-induced peripheral neuropathy (Guindon, Pharmacology Research, 2013).

[0077] In some embodiments, disclosed herein is a method of treating acute pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating acute pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. In some embodiments, disclosed herein is a method of treating inflammatory pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating inflammatory pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. In some embodiments, disclosed herein is a method of treating cancer pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating cancer pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. In some embodiments, disclosed herein is a method of treating pain caused by peripheral neuropathy, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating pain caused by peripheral neuropathy, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating acute pain, optionally comprising administering a dose from about 1 mg to about 100 mg.

Central Pain

[0078] Central pain is neuropathic pain caused by lesion or dysfunction of the central nervous system, for example, post-stroke, multiple sclerosis, neuromyelitis optica, idiopathic inflammatory transverse myelitis, spinal cord injury, brachial-radial pain syndrome, and central craniofacial pain. Exocannabinoids have demonstrated activity in

central pain associated with multiple sclerosis. A 4-week randomized double-blind placebo-controlled parallel group trial with MS and central pain using an oromucosal spray, THC/CBD, containing the CB₁ agonist delta-9-tetrahydrocannabinol and cannabidiol (another *Cannabis*-derived alcohol) showed that the active agent was superior to placebo in reducing the mean intensity of pain (NRS-11) and of sleep disturbance (Rog, Neurology, 2005, 65(6), 812-9). The same THC/CBD preparation was studied in a larger group of MS patients with central neuropathic pain utilizing a two-stage design; in the second phase of this study, the time to treatment failure (primary endpoint) statistically favored THC/CBD, as did an improvement in the Pain NRS-11 and sleep quality (Langford, J Neurol, 2013, 260(4), 984-97). Additionally, nabilone, a synthetic CB₁ agonist structurally related to THC, showed efficacy in MS-induced central neuropathic pain (Turcotte, Pain Med, 2015, 16(1), 149-59). Several studies of exocannabinoids in central pain have indicated activity, suggesting MGLL inhibitors may also have efficacy in treatment of central pain.

[0079] In some embodiments, disclosed herein is a method of treating central pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating central pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating central pain, optionally comprising administering a dose from about 1 mg to about 100 mg.

Fibromyalgia

[0080] Fibromyalgia (FM) is a common, chronic, idiopathic condition characterized by diffuse body pain and the presence of pressure allodynia. Duloxetine and pregabalin are specifically labeled for the treatment of pain in FM, and tricyclic antidepressants like amitriptyline, while not specifically labeled for FM treatment, are first-line agents. There is no clear pathological understanding of FM, and no validated preclinical model. However, several studies of exocannabinoids in FM have indicated activity, suggesting MGLL inhibitors may also have efficacy in treatment of FM. Measures of pain (e.g., NRS-11, Pain VAS) and the Fibromyalgia Impact Questionnaire (FIQ), which measures limitations in several activities of daily living impacted by FM, have demonstrated activity of drugs in FM clinical trials (Burckhardt, J Rheumatol, 1991, 18(5), 728-33; Mease, J Rheumatol, 2008, 35(3), 502-14). A survey of Spanish FM patients who were cannabis users and non-users

was performed to identify the effects of cannabis on a range of disease symptoms such as pain, stiffness, well-being, relaxation and drowsiness; perceived relief was common for pain, sleep disturbances, stiffness mood disorders and anxiety (Fiz, PLoS One, 2011, 6(4), e18440). In an 8-week, 40-patient study, compared with placebo the exocannabinoid nabilone improved pain measured on a 10 cm VAS, and improved the FIQ domain of anxiety and the FIQ total score (Skrabek, J Pain, 2008, 9(2), 164-73). In a 31-patient study, compared with amitriptyline nabilone improved the index of sleep (Insomnia Severity Index) and was judged non-inferior on measures of pain (McGill Pain Questionnaire) and the FIQ (Ware, Anesth Analg, 2010, 110(2), 604-10).

[0081] In some embodiments, disclosed herein is a method of treating fibromyalgia, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating fibromyalgia, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating fibromyalgia, optionally comprising administering a dose from about 1 mg to about 100 mg.

Migraine

[0082] Migraine is a common episodic disorder of head and facial pain. Migraine attacks can be acutely treated with NSAIDs, acetaminophen, a variety of triptans (e.g., sumatriptan), and antiemetics, but some migraine sufferers have pain unresponsive to existing treatment options. Data suggests that endocannabinoid pathways may be relevant in migraine. In patients with chronic migraine and probable analgesic-overuse headache, CSF samples showed higher levels of the endocannabinoid palmitoylethanolamide and lower levels of anandamide compared with healthy controls (Sarchielli, Neuropsychopharmacology, 2007, 32(6), 1384-90). In addition, a retrospective chart review of patients attending a medical marijuana clinic with a primary diagnosis of migraine headaches found a decrease in the frequency of migraine headaches after initiating marijuana therapy (Rhyne, Pharmacotherapy, 2016), suggesting MGLL inhibitors may also have efficacy in treatment of migraine.

[0083] In some embodiments, disclosed herein is a method of treating migraine, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments

is a method of treating migraine, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating migraine, optionally comprising administering a dose from about 1 mg to about 100 mg.

Vasoocclusive Painful Crisis in Sickle Cell Disease

[0084] Vasoocclusive painful crisis is believed to be the result of altered rheology of red blood cells (RBC) with occlusion of microcapillaries and ischemic pain in patients with sickle cell disease (SCD), a hereditary condition due to mutations in the adult hemoglobin beta gene. Vasoocclusive painful crisis in SCD is typically treated with oral or intravenous opioid analgesics; chronic opioids may be used in half of adult patients. Neuropathic pain can occur with greater age, manifest by hyperalgesia and allodynia; medicines for chronic neuropathic pain are sometimes used in these patients. A survey of patients with SCD in London identified 36% of questionnaire respondents had used cannabis in the previous year to relieve symptoms (chiefly pain) associated with SCD (Howard, Br J Haematol, 2005, 131(1), 123-8). Additionally, pain-related behaviors and neurochemical alterations in mice expressing human sickle hemoglobin were markedly improved by the cannabinoid receptor agonist CP-55940 (Kohli, Blood, 2010, 116(3), 456-65). This data suggests that MGLL inhibitors are potential therapeutic agents for treating vasoocclusive painful crisis in SCD.

[0085] In some embodiments, disclosed herein is a method of treating vasoocclusive painful crisis in sickle cell disease, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating vasoocclusive painful crisis in sickle cell disease, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating vasoocclusive painful crisis in sickle cell disease, optionally comprising administering a dose from about 1 mg to about 100 mg.

Multiple Sclerosis Symptomatic Treatment

[0086] Nearly all multiple sclerosis (MS) patients of all subtypes have one or more symptoms of spasticity, pain, disturbed sleep, bladder dysfunction, and fatigue. Disease modifying therapies do not improve symptoms. Spasticity affects over 80% of MS patients;

34% have moderate, severe, or total spasticity. Severe spasticity is related to cost and level of care, and is independently related to quality of life in MS. Two recent reviews support the use of exocannabinoids for the treatment of MS spasticity and pain (Whiting, JAMA, 2015, 313(24), 2456-2473; Hill, JAMA, 2015, 313(24), 2474-83).

[0087] An exocannabinoid preparation is an approved treatment for spasticity associated with multiple sclerosis. Sativex, an oromucosal spray mixture of the CB₁ agonist THC and another cannabis plant derived alcohol, cannabidiol, was shown to decrease self-reported spasticity related symptoms. In a pivotal trial of Sativex using a randomized withdrawal design, there was improvement with continuing Sativex in spasm frequency, sleep disruption by spasticity, subject global impression of change, carer global impression of change, and physician global impression of change. Other clinical trials have shown activity of a variety of exocannabinoids in spasticity due to multiple sclerosis (Zajicek, Lancet, 2003, 362(9395), 1517-26; Collin, Eur J Neurol, 2007, 14(3), 290-6; Collin, Neurol Res, 2010, 32(5), 451-9). These parallel group studies exemplify the clinical trial design and endpoints that could be used to show a MGLL benefits spasticity in MS.

[0088] In some embodiments, disclosed herein is a method of treating spasticity or pain associated with multiple sclerosis, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating spasticity or pain associated with multiple sclerosis, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating spasticity or pain associated with multiple sclerosis, optionally comprising administering a dose from about 1 mg to about 100 mg.

Functional Chest Pain

[0089] Functional chest pain, sometimes called non-GERD, non-cardiac chest pain, is a functional gastrointestinal disorder where discomfort of upper GI structures is perceived in the chest. In addition to consuming medical resources to rule out other treatable conditions, functional chest pain causes distress for patients. It may be treated with tricyclic antidepressants or serotonin norepinephrine reuptake inhibitors, but not all patients respond. In patients with functional chest pain, a syndrome ascribed to GI hypersensitivity, the exocannabinoid dronabinol improved chest pain symptoms and raised sensory threshold for balloon distension of the esophagus in a placebo-controlled 4 week study (Malik, Dis

Esophagus, 2016, online pub. DOI: 10.1111/dote.12455), suggesting MGLL inhibitors may also have efficacy in treatment of functional chest pain.

[0090] In some embodiments, disclosed herein is a method of treating functional chest pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating functional chest pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating functional chest pain, optionally comprising administering a dose from about 1 mg to about 100 mg.

Rheumatoid Arthritis and Osteoarthritis

[0091] CB₁ and CB₂ receptors were found to be present in the synovia of rheumatoid arthritis (RA) and osteoarthritis (OA) patients. The endocannabinoids anandamide and 2-AG were identified in synovial fluid of RA and OA patients, but not in normal volunteers (Richardson, Arthritis Res Ther, 2008, 10(2), R43). In addition, a small RA patient trial with nabiximols (THC/CBD oromucosal spray) showed improved pain on movement at rest, improved sleep, and an improvement in the standard RA Disease Activity Score in 28 joints (DAS28) (Blake, Rheumatology (Oxford), 2006, 45(1), 50-2). These data predict that MGLL may be an important therapeutic target for the treatment of pain and inflammation in RA and OA.

[0092] In some embodiments, disclosed herein is a method of treating rheumatoid arthritis or osteoarthritis, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating rheumatoid arthritis or osteoarthritis, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. In some embodiments, disclosed herein is a method of treating rheumatoid arthritis pain or osteoarthritis pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating rheumatoid arthritis pain or osteoarthritis pain, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is

from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating rheumatoid arthritis or osteoarthritis, optionally comprising administering a dose from about 1 mg to about 100 mg.

Alzheimer's Disease

[0093] Alzheimer's disease (AD) is the most common cause of dementia, affecting ~5.3 million people in the US. Agitation and aggression are risk factors for institutionalization of patients with dementia. The exocannabinoid dronabinol improved anorexia and decreased agitation in AD patients (Volicer, Int J Geriatr Psychiatry, 1997, 12(9), 913-9) and reduced nighttime agitation in AD patients (Walther, J Clin Psychopharmacol, 2011, 31(2), 256-8). A MGLL inhibitor could be tested in either a parallel group or a crossover study of selected AD patients with dementia and agitation. As an example, the CIT-AD trial measured agitation in patients randomized to psychosocial intervention plus either placebo or citalopram for 9 weeks (Porsteinsson, JAMA, 2014, 311(7), 682-91).

[0094] In some embodiments, disclosed herein is a method of treating agitation or aggression associated with Alzheimer's disease, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating agitation or aggression associated with Alzheimer's disease, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating agitation or aggression associated with Alzheimer's disease, optionally comprising administering a dose from about 1 mg to about 100 mg.

Functional Dyspepsia

[0095] Functional dyspepsia (FD) is one of the most common gastrointestinal disorders encountered in clinical practice. Several pathophysiological mechanisms have been proposed to underlie symptom generation in FD, including visceral hypersensitivity due to central or peripheral sensitization, low-grade inflammatory states, altered secretion of gastrointestinal hormones, genetic predisposition, and abnormal gastric emptying or accommodation. Gastric accommodation in healthy humans is inhibited by administration of the CB₁ receptor antagonist rimonabant (Ameloot, Aliment Pharmacol Ther, 2010, 31(10), 1123-31). In addition, research supports the hypothesis that the function of the

endocannabinoid system is altered in FD patients; hence, it is inferred that MGLL inhibition, by elevating 2-AG, in turn activating the CB₁ receptor, will increase gastric accommodation and lessen symptoms of functional dyspepsia (Ly, Psychother Psychosom, 2015, 84(3), 149-58).

[0096] In some embodiments, disclosed herein is a method of treating functional dyspepsia, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating functional dyspepsia, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating functional dyspepsia, optionally comprising administering a dose from about 1 mg to about 100 mg.

Inflammatory Bowel Disease

[0097] Inflammatory bowel disease (IBD) involves chronic inflammation of all or part of the digestive tract. IBD primarily includes ulcerative colitis and Crohn's disease. Both usually involve severe diarrhea, pain, fatigue and weight loss. IBD can be debilitating and sometimes leads to life-threatening complications. MGLL inhibition was protective in a mouse model of IBD (Alhouayek, FASEB, 2011, 2711-2721).

[0098] In some embodiments, disclosed herein is a method of treating inflammatory bowel disease, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating inflammatory bowel disease, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating inflammatory bowel disease, optionally comprising administering a dose from about 1 mg to about 100 mg.

Skeletal Muscle Contusion

[0099] Skeletal muscle contusion indicates a direct, blunt, compressive force to a muscle. Contusions are one of the most common sports-related injuries. The severity of contusions ranges from simple skin contusions to muscle and bone contusions to internal organ contusions. MGLL inhibition demonstrated anti-inflammatory effects in a rat skeletal

muscle contusion model (Jiang, European Journal of Pharmacology, 2015, online pub. dx.doi.org/10.1016).

[00100] In some embodiments, disclosed herein is a method of treating a skeletal muscle contusion, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating a skeletal muscle contusion, in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg. Disclosed also herein is Compound 1, or a pharmaceutically acceptable salt thereof, for use in a method of treating a skeletal muscle contusion of the human or animal body, optionally comprising administering a dose from about 1 mg to about 100 mg.

Additional Methods

[00101] Disclosed herein are methods of optimizing therapeutic efficacy for treatment of inflammation or neuropathic pain in a patient in need thereof, comprising (a) administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof; (b) measuring the concentration of plasma 2-AG in the patient; and (c) administering an increased or decreased amount of Compound 1 as indicated by the concentration of plasma 2-AG. Disclosed also herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in a method for optimizing therapeutic efficacy of a treatment of inflammation or neuropathic pain in a patient, said method comprising (a) administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof; (b) measuring the concentration of plasma 2-AG in the patient; and (c) administering an increased or decreased amount of Compound 1 as indicated by the concentration of plasma 2-AG.

[00102] Disclosed herein are methods of optimizing therapeutic efficacy for treatment of inflammation or neuropathic pain in a patient in need thereof, comprising (a) administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof; (b) measuring the percentage of MGLL covalently attached to a fragment of Compound 1 in PBMCs from the patient; and (c) administering an increased or decreased amount of Compound 1 as indicated by the percentage of MGLL covalently attached to a fragment of Compound 1 in plasma. Disclosed also herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in a method for optimizing therapeutic efficacy of a treatment of inflammation or neuropathic pain in a

patient, said method comprising (a) administering to the patient in need thereof a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof; (b) measuring the percentage of MGLL covalently attached to a fragment of Compound 1 in PBMCs from the patient; and (c) administering an increased or decreased amount of Compound 1 as indicated by the percentage of MGLL covalently attached to a fragment of Compound 1 in plasma.

[00103] Disclosed herein are methods of increasing the concentration of plasma 2-AG in a subject using an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, wherein the concentration of plasma 2-AG in a subject is increased by at least 2-fold. Disclosed also herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in a method of therapy of increasing the concentration of plasma 2-AG in a subject, by administering an effective dose of Compound 1 or a pharmaceutically acceptable salt thereof, wherein the concentration of plasma 2-AG in the subject is increased by at least 2-fold. In some embodiments, the concentration of plasma 2-AG in a subject is increased by at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, or at least 10-fold. In some embodiments, the effective dose is from about 1 mg to about 500 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is from about 2 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is about 10 mg to about 160 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is about 2 mg to about 20 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is administered orally.

[00104] Also disclosed herein are methods of binding MGLL with Compound 1 in PBMCs in a subject after administration of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject, wherein a fragment of Compound 1 is covalently attached to at least 30% MGLL in PBMCs. Disclosed also herein is Compound 1 or a pharmaceutically acceptable salt thereof, for use in any one of the methods of therapy disclosed herein, wherein after administration in a subject of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, a fragment of Compound 1 is covalently attached to at least 30% MGLL in PBMCs of the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%, MGLL in PBMCs. In some embodiments, the effective dose is from about 1 mg to about 500 mg of

Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is from about 2 mg to about 400 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is about 10 mg to about 160 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is about 2 mg to about 20 mg of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the effective dose is administered orally.

Dosage and Plasma AUC

[00105] In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg, including increments therein.

[00106] In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 500 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 450 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt

thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 1 mg to about 15 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 150 mg. In some

embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 2 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 160 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 75 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is from about 10 mg to about 25 mg.

[00107] In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered orally. In some embodiments, the effective dose is taken with food. In some embodiments, the effective dose is taken without food. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered once per day. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered

twice per day. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered three times per day. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered four times per day. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered once every two days. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered once every three days. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered once every four days. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered once every five days. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered once every six days. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods and medical uses disclosed herein is administered once per week.

[00108] In some embodiments, a blood sample is collected from a subject after administration of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the blood sample is analyzed for Compound 1 quantification.

[00109] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.05 \mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.01 \mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.1 \mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.2 \mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a plasma $AUC_{0-\infty}$ of Compound 1 is at least $0.3 \mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a plasma $AUC_{0-\infty}$ of Compound 1 is at least

[illegible]

[illegible]

[illegible]

[illegible]

provides a steady state plasma AUC_{0-inf} of Compound 1 is at least $1.8 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is at least $2.0 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is at least $2.2 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is at least $2.4 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is at least $2.6 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is at least $2.8 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is at least $3.0 \mu M \cdot hr$.

[00112] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.01 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.05 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.1 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.15 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.2 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.3 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.4 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma AUC_{0-inf} of Compound 1 is about 0.5 $\mu M \cdot hr$ to about 3.0 $\mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically

[illegible]

is about 0.1 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 is about 0.15 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 is about 0.2 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 is about 0.3 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 is about 0.4 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 is about 0.5 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 is about 0.7 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, to a subject provides a steady state plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 is about 1.0 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$.

[00113] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 of at least 0.05 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 of at least 0.01 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 of at least 0.1 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 of at least 0.2 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 of at least 0.3 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average

plasma AUC_{0-inf} of Compound 1 of at least 0.4 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 0.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 0.6 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 0.7 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 0.8 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 0.9 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 1.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 1.2 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 1.4 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 1.6 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 1.8 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma AUC_{0-inf} of Compound 1 of at least 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments,

administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of at least $2.2 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of at least $2.4 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of at least $2.6 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of at least $2.8 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of at least $3.0 \mu M \cdot hr$.

[00114] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about $0.01 \mu M \cdot hr$ to about $3.0 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about $0.05 \mu M \cdot hr$ to about $3.0 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about $0.1 \mu M \cdot hr$ to about $3.0 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about $0.15 \mu M \cdot hr$ to about $3.0 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about $0.2 \mu M \cdot hr$ to about $3.0 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about $0.3 \mu M \cdot hr$ to about $3.0 \mu M \cdot hr$. In some embodiments, administration of Compound 1, or a

pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.4 $\mu\text{M}\cdot\text{hr}$ to about 3.0 $\mu\text{M}\cdot\text{hr}$. **In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.5 $\mu\text{M}\cdot\text{hr}$ to about 3.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.7 $\mu\text{M}\cdot\text{hr}$ to about 3.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 1.0 $\mu\text{M}\cdot\text{hr}$ to about 3.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.01 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.05 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.1 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.15 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.2 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.3 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.4 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein**

produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.5 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.7 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 1.0 $\mu\text{M}\cdot\text{hr}$ to about 2.5 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.01 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.05 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.1 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.15 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.2 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.3 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.4 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.5 $\mu\text{M}\cdot\text{hr}$ to about 2.0 $\mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $AUC_{0-\infty}$ of Compound 1 of about 0.7

$\mu\text{M}\cdot\text{hr}$ to about $2.0 \mu\text{M}\cdot\text{hr}$. In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $\text{AUC}_{0-\text{inf}}$ of Compound 1 of about $1.0 \mu\text{M}\cdot\text{hr}$ to about $2.0 \mu\text{M}\cdot\text{hr}$.

[00115] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce in a human subject group an average plasma $\text{AUC}_{0-\text{inf}}$ of about $0.01 \mu\text{M}\cdot\text{hr}$, $0.05 \mu\text{M}\cdot\text{hr}$, $0.1 \mu\text{M}\cdot\text{hr}$, $0.15 \mu\text{M}\cdot\text{hr}$, about $0.2 \mu\text{M}\cdot\text{hr}$, about $0.3 \mu\text{M}\cdot\text{hr}$, about $0.4 \mu\text{M}\cdot\text{hr}$, about $0.5 \mu\text{M}\cdot\text{hr}$, about $0.6 \mu\text{M}\cdot\text{hr}$, about $0.7 \mu\text{M}\cdot\text{hr}$, about $0.8 \mu\text{M}\cdot\text{hr}$, about $0.9 \mu\text{M}\cdot\text{hr}$, about $1.0 \mu\text{M}\cdot\text{hr}$, about $1.1 \mu\text{M}\cdot\text{hr}$, about $1.2 \mu\text{M}\cdot\text{hr}$, about $1.3 \mu\text{M}\cdot\text{hr}$, about $1.4 \mu\text{M}\cdot\text{hr}$, about $1.5 \mu\text{M}\cdot\text{hr}$, about $1.6 \mu\text{M}\cdot\text{hr}$, about $1.7 \mu\text{M}\cdot\text{hr}$, about $1.8 \mu\text{M}\cdot\text{hr}$, about $1.9 \mu\text{M}\cdot\text{hr}$, about $2.0 \mu\text{M}\cdot\text{hr}$, about $2.1 \mu\text{M}\cdot\text{hr}$, about $2.2 \mu\text{M}\cdot\text{hr}$, about $2.3 \mu\text{M}\cdot\text{hr}$, about $2.4 \mu\text{M}\cdot\text{hr}$, about $2.5 \mu\text{M}\cdot\text{hr}$, about $2.6 \mu\text{M}\cdot\text{hr}$, about $2.7 \mu\text{M}\cdot\text{hr}$, about $2.8 \mu\text{M}\cdot\text{hr}$, about $2.9 \mu\text{M}\cdot\text{hr}$, about $3.0 \mu\text{M}\cdot\text{hr}$, about $3.1 \mu\text{M}\cdot\text{hr}$, about $3.2 \mu\text{M}\cdot\text{hr}$, about $3.3 \mu\text{M}\cdot\text{hr}$, about $3.4 \mu\text{M}\cdot\text{hr}$, about $3.5 \mu\text{M}\cdot\text{hr}$, about $3.6 \mu\text{M}\cdot\text{hr}$, about $3.7 \mu\text{M}\cdot\text{hr}$, about $3.8 \mu\text{M}\cdot\text{hr}$, about $3.9 \mu\text{M}\cdot\text{hr}$, or about $4.0 \mu\text{M}\cdot\text{hr}$ after administration of Compound 1 to the subject.

[00116] In some embodiments, urine is collected from a subject after administration of Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the urine is analyzed for urinary Compound 1 quantification and urinary excretion characterization. In further embodiments, the urine is analyzed for qualitative metabolite characterization.

[00117] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce little to no effect on mood state of the subject or patient. In some embodiments, pre- and post-dose fluctuations in mood of the subject or patient are assessed using the short-version (30 items) of the Profile of Mood States (POMS Brief Form). In some embodiments, POMS data is used to evaluate potential Compound 1 dose-related effects on mood.

[00118] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce little to no effect on cognitive function of the subject or patient. In some embodiments, effects on cognitive function are evaluated using a battery of standardized and validated computerized tests (Cogstate Battery). This battery includes the following tests: Groton Maze Learning Test (GMLT), Detection (DET), Identification (IDN), One Card Learning (OCL), and ONB (One Back) Tasks. In some embodiments, the subject or patient performs this battery pre-

dose, and at the protocol-specified intervals post-dose in order to evaluate potential Compound 1 dose-related effects on cognition, problem solving/reasoning, processing speed, attention/vigilance and visual recognition memory.

[00119] In some embodiments, administration of Compound 1, or a pharmaceutically acceptable salt thereof, in the methods and medical uses disclosed herein produce mild to no effect on the patient's or subject's Cutaneous Thermal Thresholds (CTT).

[00120] Target Engagement

[00121] In some embodiments, plasma concentration of Compound 1 is measured from a sample of blood from the subject after administration of Compound 1, or a pharmaceutically acceptable salt thereof.

[00122] In some embodiments, the blood sample from the subject is evaluated for MGLL activity. In some embodiments, MGLL activity is evaluated by measurement of plasma 2-AG concentration. 2-AG is an endogenous MGLL substrate. Inhibition of MGLL *in vivo* in preclinical species is associated with increases in 2-AG concentrations (in the brain, as well as in the peripheral blood). In some embodiments, plasma 2-AG concentration is measured using an *in vitro* assay. In some embodiments, plasma 2-AG concentration is measured using a fit-for-purpose mass spectrometry assay. In some embodiments, plasma 2-AG concentrations are measured from the same blood samples that are collected for the evaluation of Compound 1 plasma concentrations.

[00123] Since plasma 2-AG concentrations in humans are known to undergo diurnal fluctuation [Hanlon *et al.*, "Circadian rhythm of circulating levels of the endocannabinoid 2-arachidonoylglycerol", *J. Clin. Endocrinol. Metab.* 100:220-226, (2015)], plasma 2-AG data from both recipients of the hydrochloride salt of Compound 1 and recipients of placebo are used to evaluate the dose-related effects of the hydrochloride salt of Compound 1. In some embodiments, average plasma 2-AG concentration in an untreated subject is about ~1.8 ng/mL (~4.8 nM). In some embodiments, plasma 2-AG concentrations in untreated subjects range from about 0.5 ng/mL to about 5 ng/mL.

[00124] In some embodiments, plasma 2-AG concentration in a subject increases at least 2-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases at least 3-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases at least 4-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration

in a subject increases at least 5-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases at least 6-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases at least 7-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases at least 8-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases at least 9-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases at least 10-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof.

[00125] In some embodiments, plasma 2-AG concentration in a subject increases about 2-fold to about 10-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases about 2-fold to about 3-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases about 2-fold to about 4-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases about 2-fold to about 5-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases about 2-fold to about 6-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases about 2-fold to about 7-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases about 5-fold to about 7-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject increases about 5-fold to about 10-fold after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof.

[00126] In some embodiments, plasma 2-AG concentration in a subject is about 1 ng/mL to about 10 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is about 1.5 ng/mL to about 15 ng/mL after administration to the subject of

Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is about 2.6 ng/mL to about 15 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is about 3.0 ng/mL to about 18.0 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is about 4.0 ng/mL to about 15 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is about 5.0 ng/mL to about 15 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof.

[00127] In some embodiments, plasma 2-AG concentration in a subject is at least 2.6 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 5.4 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 7.2 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 9.0 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 10.8 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 12.6 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 14.4 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 16.2 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof. In some embodiments, plasma 2-AG concentration in a subject is at least about 18.0 ng/mL after administration to the subject of Compound 1, or a pharmaceutical acceptable salt thereof.

[00128] In some embodiments, the residual plasma (*i.e.*, after completion and unblinding of the study) is assayed for the presence of one or more other endogenous lipid mediators (*e.g.*, other monoacylglycerol lipids and anandamide (AEA), the other major endogenous cannabinoid and primary substrate of FAAH).

[00129] In some embodiments, the blood sample from the subject is evaluated for peripheral blood mononuclear cell (PBMC) MGLL activity. Previous *in vitro* studies have demonstrated the presence of measurable MGLL activity in PBMCs prepared from healthy human donors. In some embodiments, the pharmacologic activity of exogenously added MGLL inhibitors in these PBMC preparations is readily quantified using activity-based protein profiling (ABPP) electrophoretic techniques, or by substrate-based assays. In some embodiments, MGLL target engagement in PBMCs is measured in PBMCs collected from subjects before, and at specified time intervals after administration of study drug using a fit-for-purpose substrate assay. In some embodiments, the dose- and exposure-related effects of Compound 1 on PBMC MGLL activity is evaluated. In some embodiments, a mass spectroscopy-based substrate assay is used to evaluate MGLL activity in PBMCs.

[00130] In some embodiments, a fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 40% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 50% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 55% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 60% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 65% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 70% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 75% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 80% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 85% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 90% of MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, a fragment of Compound 1 is covalently attached to at least 95% of

MGLL in PBMCs from a subject after administration of Compound 1 to the subject. In some embodiments, measurement of fragments of Compound 1 covalently attached to MGLL in PBMCs in a subject is performed using an *in vitro* assay.

[00131] In some embodiments, the residual PBMC fractions (*i.e.*, after completion and unblinding of the study) are also assayed for target engagement using ABPP techniques. The easy accessibility of PBMC in healthy volunteers facilitates the measurement of MGLL target engagement in the peripheral blood of healthy volunteers.

[00132] In some embodiments, a blood sample from a subject is also analyzed for one or more endogenous lipids other than or in addition to 2-AG. In further embodiments, the one or more endogenous lipids include, but are not limited to, anandamide and other monoacylglycerol species. In some embodiments, the one or more endogenous lipids is anandamide.

[00133] **Pharmaceutical Compositions**

[00134] Disclosed herein are pharmaceutical compositions for the treatment of inflammation or neuropathic pain, wherein each of the pharmaceutical compositions comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00135] Further disclosed herein are pharmaceutical compositions for the treatment of inflammation or neuropathic pain, wherein each of the pharmaceutical compositions comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75

mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg, including increments therein.

[00136] Further disclosed herein are pharmaceutical compositions for the treatment of inflammation or neuropathic pain, wherein each of the pharmaceutical compositions comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 450 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 25 mg. In some embodiments, an effective dose of Compound

1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 15 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 160 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 75 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically

acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 25 mg.

[00137] Disclosed herein are pharmaceutical compositions for the treatment of neuropathic pain, wherein each of the pharmaceutical compositions comprise an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00138] Disclosed herein are pharmaceutical compositions for the treatment of neuropathic pain, wherein each of the pharmaceutical compositions comprise an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00139] Further disclosed herein is a pharmaceutical composition for the treatment of neuropathic pain, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85

mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg, including increments therein.

[00140] Further disclosed herein is a pharmaceutical composition for the treatment of neuropathic pain, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 450 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt

thereof, administered in the methods disclosed herein is from about 1 mg to about 15 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 160 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 75 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the

methods disclosed herein is from about 10 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 25 mg.

[00141] Disclosed herein are pharmaceutical compositions for the treatment of inflammation, wherein each of the pharmaceutical compositions comprise an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00142] Further disclosed herein is a pharmaceutical composition for the treatment of inflammation, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg, including increments therein.

[00143] Further disclosed herein is a pharmaceutical composition for the treatment of inflammation, wherein the pharmaceutical composition comprises an effective dose of

Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 450 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 15 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 250 mg. In some embodiments, an effective dose of Compound

1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 160 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 75 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 25 mg.

[00144] Disclosed herein are pharmaceutical compositions for the treatment of inflammation or neuropathic pain, wherein each of the pharmaceutical compositions consist essentially of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In

some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00145] Disclosed herein are pharmaceutical compositions for the treatment of neuropathic pain, wherein each of the pharmaceutical compositions consist essentially of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00146] Disclosed herein are pharmaceutical compositions for the treatment of inflammation, wherein each of the pharmaceutical compositions consist essentially of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00147] Disclosed herein are pharmaceutical compositions for the treatment of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome, wherein each of the pharmaceutical compositions comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00148] Disclosed herein are pharmaceutical compositions for the treatment of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel

Syndrome, wherein each of the pharmaceutical compositions comprise an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00149] Further disclosed herein is a pharmaceutical composition for the treatment of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg, including increments therein.

[00150] Further disclosed herein is a pharmaceutical composition for the treatment of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome, wherein the pharmaceutical composition comprises an effective dose of

Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 450 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 15 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 250 mg. In some embodiments, an effective dose of Compound

1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 160 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 75 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 25 mg.

[00151] Disclosed herein are pharmaceutical compositions for the treatment of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome, wherein each of the pharmaceutical compositions consist essentially of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400

mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00152] Disclosed herein are pharmaceutical compositions for the treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein each of the pharmaceutical compositions comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00153] Disclosed herein are pharmaceutical compositions for the treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein each of the pharmaceutical compositions comprise an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00154] Further disclosed herein is a pharmaceutical composition for the treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a

pharmaceutically acceptable excipient, wherein the effective dose is about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg, including increments therein.

[00155] Further disclosed herein is a pharmaceutical composition for the treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein the pharmaceutical composition comprises an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 450 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered

in the methods disclosed herein is from about 1 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 1 mg to about 15 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 400 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 350 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 150 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 2 mg to about 25 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed

herein is from about 10 mg to about 300 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 250 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 200 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 160 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 100 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 75 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 50 mg. In some embodiments, an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, administered in the methods disclosed herein is from about 10 mg to about 25 mg.

[00156] Disclosed herein are pharmaceutical compositions for the treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein each of the pharmaceutical compositions consist essentially of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg. In some embodiments, the effective dose is from about 2 mg to about 400 mg. In some embodiments, the effective dose is from about 10 mg to about 160 mg. In some embodiments, the effective dose is from about 2 mg to about 100 mg. In some embodiments, the effective dose is from about 2 mg to about 50 mg. In some embodiments, the effective dose is from about 2 mg to about 20 mg.

[00157] The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

EXAMPLES

Example 1. *In vitro* pharmacology

[00158] Compound 1 was a potent inhibitor of human, mouse, rat, and dog MGLL with an $IC_{50} < 30$ nM in all species. *In vitro* potency was determined using activity-based protein

profiling (ABPP) which is a functional proteomic technology that uses chemical probes to covalently modify enzyme active sites in an activity-dependent manner (*e.g.*, only catalytically active enzymes will react and become labeled with the ABPP probe). Identification of the proteins that were labeled by the probes was accomplished using polyacrylamide gel electrophoresis or mass spectrometry. *In vitro* treatment of tissue or cell homogenates with Compound 1 followed by incubation with probe, gel electrophoresis, and fluorescence imaging, allowed for the direct visualization and quantitation of the targets of Compound 1.

[00159] The inhibitory potency of Compound 1 towards MGLL in mouse, rat, dog, and human brain tissue and in lysates prepared from 2 human cell lines (PC3 prostate cancer cells and human embryo kidney [HEK]293T cells expressing recombinant hMGLL) was calculated as the IC₅₀ following a 30-minute pre-incubation. The IC₅₀ values are summarized in Table 1. MGLL migrates as multiple molecular weight species of approximately 34 kDa by gel electrophoresis. Compound 1 displays equivalent inhibitory potency against all MGLL isoforms.

[00160] **Table 1.** *In vitro* potency of Compound 1 against MGLL in mouse, rat, dog, and human tissue and cell homogenates determined by ABPP

Species	Source	MGLL IC ₅₀ (μ M)
Mouse	Brain*	0.027 $\pm$ 0.003
Rat	Prefrontal Cortex [†]	0.026 $\pm$ 0.006
Dog	Prefrontal Cortex [†]	0.012 $\pm$ 0.002
Human	PC3 Cells [‡]	0.014 $\pm$ 0.005
	Prefrontal Cortex [†]	0.021 $\pm$ 0.004
	Recombinant [‡]	0.008 $\pm$ 0.005

Abbreviations: ABPP = activity-based protein profiling is a functional proteomic technology that uses chemical probes that react with mechanistically related classes of enzymes; IC₅₀ = concentration producing 50% inhibition; MGLL = monoacylglycerol lipase.

Additional information: Compound 1 (0-10 μ M) was pre-incubated with the listed source material for 30 min at 37 °C prior to ABPP analysis. Data represent mean $\pm$ standard error of the mean (SEM) from several independent experiments: * *n*=10, [†] *n*=3, [‡] *n*=2.

[00161] The activity of Compound 1 was also assessed in human brain tissue using a mass spectrometry (MS)-based 2-AG substrate assay. In homogenates prepared from a human brain cortex sample, Compound 1 inhibited 94% of the conversion of 2-AG into AA with an IC₅₀ of 1.7 nM. Cellular potency was evaluated by gel-based ABPP in intact human

PC3 prostate cancer cells where Compound 1 inhibited MGLL activity with an IC_{50} of 2.2 nM.

Example 2. *In vivo* pharmacology

[00162] *A. Relationship Among MGLL Target Engagement, 2-AG Concentrations, and Compound 1 Concentrations*

[00163] Occupancy and inhibition of protein active sites by small molecules is referred to as target engagement (*i.e.*, a proximal marker of or how robustly a drug interacts with the target). Target engagement of MGLL by Compound 1 was measured using PET in non-human primates and ABPP in rodents and dogs. MGLL target engagement inhibits the hydrolysis of 2-AG, elevating tissue 2-AG concentrations, which can be measured in rodent tissues and fluids by MS. Elevation of 2-AG results in enhanced cannabinoid receptor signaling and physiological responses. The objective of these studies was to measure MGLL target engagement, 2-AG concentrations, and Compound 1 concentrations following Compound 1 administration in animals.

[00164] MGLL target engagement in the brain of rhesus monkeys was evaluated using a labeled form of a MGLL inhibitor. In rhesus monkeys, this labeled MGLL inhibitor demonstrated brain penetrance and regional distribution consistent with the known expression of MGLL in CB_1 -containing neurons. MGLL occupancy by Compound 1 in the rhesus brain was evaluated using a blockade protocol comparing the labeled MGLL inhibitor binding at baseline and again following administration of Compound 1. Single-dose IV administration of Compound 1 (0.01-1 mg/kg, 90 min prior to PET tracer, 2 animals) engaged MGLL in the rhesus brain with an ED_{50} of 0.047 ± 0.025 mg/kg (*see FIG. 1*).

[00165] An oral-equivalent ED_{50} dose for target engagement (but not for efficacy) was calculated from single-dose intravenous administration using a fraction absorbed factor of 0.2 (20% bioavailability).

[00166] ABPP analysis of tissues and cells from rodents treated with Compound 1 allowed direct visualization and quantitation of MGLL inhibition *in vivo*. Single-dose oral gavage (PO) administration of Compound 1 (up to 30 mg/kg, 4 hours, $n=3-10$, 4 independent experiments) to rats inhibited MGLL activity in the brain with an average ED_{50} of 0.6 mg/kg. Dose-dependent inhibition of MGLL activity was also observed in rat liver (ED_{50} of 0.1 mg/kg), heart (ED_{50} of 0.08 mg/kg), and PBMC (ED_{50} of 0.1 mg/kg).

[00167] Inhibition of MGLL causes accumulation of 2-AG in the rodent brain and periphery. Rat forebrain 2-AG concentrations increased ≥ 10 -fold over control levels

following single oral doses of Compound 1 (up to 30 mg/kg, 4 hours, $n=3-10$, 3 independent experiments) and were inversely related to brain MGLL activity. Brain 2-AG concentrations increased with an average ED_{50} value of 1.3 mg/kg. The reduced potency for 2-AG accumulation (ED_{50} of 1.3 mg/kg) versus MGLL inhibition (ED_{50} value of 0.6 mg/kg) reflects the observation that inhibition of MGLL activity by approximately 50% is required before 2-AG accumulation is observed. Rat brain levels of the endocannabinoid anandamide were not elevated by Compound 1, suggesting that Compound 1 at these concentrations does not inhibit FAAH the primary anandamide hydrolase. Concentration of 2-AG in rat plasma and liver increased by 7-fold and approximately 3-to 5-fold, respectively, following single oral doses of Compound 1. Brain, liver, and blood Compound 1 concentrations increased with increasing doses of Compound 1 and were positively associated with MGLL inhibition and 2-AG concentrations.

[00168] Compound 1 caused similar dose-dependent effects on MGLL activity, 2-AG concentrations, and Compound 1 concentrations in mice. Single-dose PO administration of Compound 1 (2-32 mg/kg, 4 hours, $n=3$) inhibited MGLL activity in the mouse brain and liver with ED_{50} values of 1.4 mg/kg and 0.5 mg/kg, respectively. Mouse brain 2-AG concentrations increased up to 30-fold following Compound 1 treatment.

[00169] Using fixed exponent allometric scaling, the projected human oral ED_{50} -equivalent dose based on the rat and monkey ED_{50} data, ranges from 4.4 to 8.6 mg.

[00170] *B. Time Course of Compound 1 Concentrations, MGLL Inhibition, and 2-AG Concentrations and Recovery of MGLL Activity*

[00171] Time-course effects of a single dose of Compound 1 (0.5-10 mg/kg, up to 144 hour postdose, $n=3$, 3 independent experiments) were evaluated in rats. In the rat brain, Compound 1 displayed time-dependent effects on MGLL activity. Compound concentrations of Compound 1 were positively correlated with inhibition of MGLL activity and levels of 2-AG (*see FIG. 2A-C*). Near-maximal MGLL inhibition and 2-AG accumulation was observed 4 hours after dosing, supporting the use of a 4-hour timepoint for behavioral studies.

[00172] After elimination of Compound 1 from the rat brain (*i.e.*, to levels below the limit of quantitation [BLQ]), MGLL activity recovered at an average rate of approximately 2% per hour (*see FIG. 2D*). The recovery rate of MGLL activity in the rat brain is similar to that observed following covalent MGLL inhibition in other rat tissues and in cultured human cells. Once MGLL activity in the rat brain recovered to approximately 50% of pre-treatment activity, brain 2-AG concentrations returned to basal levels (*see FIG. 2B*).

[00173] Similar time-dependent effects on brain MGLL activity, 2-AG concentrations, and Compound 1 concentrations were observed following single dose Compound 1 in mice.

[00174] *C. Efficacy in Rodent Models of Pain*

[00175] The rat formalin paw test was used as the primary preclinical model to assess the PK/PD relationship for Compound 1 and inform human dose prediction. The formalin paw test is a model of pain induced by local injection of formalin into the hind paw producing an early response due to direct stimulation of nociceptors and a delayed response driven by inflammation and central sensitization. In studies performed with Compound 1, nociception was tracked by scoring the duration and frequency of paw licking using an automated system.

[00176] Single-dose administration of Compound 1 (up to 10 mg/kg, PO, 4 hours pre-test, $n=10$, 2 independent experiments) caused dose-dependent antinociceptive effects in formalin-challenged rats and reduced paw licking behavior in both the early (Phase 1) and delayed (Phase 2) phases (see **FIG. 3B**). The Phase 2 ED_{50} of 0.5 mg/kg was used to assess the PK/PD relationship. Similar antinociceptive responses were observed with a single dose of the alpha-2, delta-1 calcium channel blocker pregabalin (30 mg/kg, PO, $n=10$), which is a clinically effective analgesic agent used for the treatment of neuropathic pain. The PK/PD relationship for Compound 1 in the rat formalin model is depicted in **FIG. 3A-D**, along with brain MGLL activity and 2-AG concentrations. This relationship demonstrates that Compound 1 achieves efficacy in the rat formalin test at doses that partially inhibit MGLL in the brain and cause sub-maximal increases in brain 2-AG concentrations. The ED_{50} of 0.5 mg/kg in Phase 2 of the rat formalin test corresponds to brain Compound 1 concentrations of 5 nM, blood Compound 1 concentrations of 7 nM, approximately 40% inhibition of brain MGLL activity, and approximately 3-fold elevations in brain 2-AG concentrations.

[00177] The effects of multiple-dose administration of Compound 1 (0.5-10 mg/kg, 5 days QD, $n=10$) in the rat formalin model were investigated in a single study. Single and repeated administration of Compound 1 at a dose that partially inhibited MGLL (1 mg/kg) numerically reduced pain behaviors to a similar extent, though effects in the repeat dose group were not statistically different from vehicle.

[00178] The ED_{50} for Compound 1 exposure associated with efficacy in the rat **formalin nocifensive model** was $0.4 \mu\text{M}\cdot\text{hr}$. Single oral ED_{50} doses for efficacy (nocifensive paw licking behavior) and target engagement (by *ex vivo* activity-based protein profiling) were of similar magnitude. The ED_{50} dose for nocifensive efficacy was also a minimally-efficacious dose. At the ED_{50} dose in rats, and at oral doses 20-fold higher (the

highest dose of Compound 1 evaluated in the formalin challenge model), overt behavioral or locomotor perturbations apart from the observed anti-nocifensive behaviors were not apparent. Rat brain 2-AG concentrations became measurably elevated only once MGLL activity is inhibited by greater than approximately 40-50%.

Example 3. Determination of MGLL Inhibition in rat PBMCs and plasma 2-AG levels with Compound 1

[00179] Rats were administered single PO doses of Compound 1 (up to 30 mg/kg, 4 h, $n=2-3$). MGLL activity in rat PBMCs decreased dose-dependently with a median effective dose (ED₅₀) of 0.07 mg/kg and plasma 2-AG levels increased by up to 7-fold (*see* FIG. 4A-B). MGLL activity was assessed by ABPP analysis in PBMC lysates and plasma 2-AG concentrations were measured by liquid chromatography tandem mass spectrometry (LC-MS/MS).

Example 4. Determination of MGLL Inhibition in human PBMCs with Compound 1

[00180] MGLL activity in human PBMCs can be readily assessed by ABPP analysis (*see* FIG. 4A) or by a mass spectrometry-based 2-AG substrate assay that measures the formation of AA product (*see* FIG. 5B). Incubation of Compound 1 (0.0003-1000 nM, 30 min, 37°C) in human whole blood obtained from two healthy human donors inhibits MGLL activity in isolated PBMCs with an IC₅₀ of 47 nM (*see* FIG. 5B).

Example 5. Capsule formulation

[00181] The hydrochloride salt of Compound 1 is formulated as powder-filled, gelatin capsules containing 2.14, 10.72, and 53.60 mg of hydrochloride salt which are equivalent to 2, 10, and 50 mg of Compound 1, respectively (salt factor = 1.07). The gelatin capsule shells used are size 2 and the color of both cap and body is Swedish Orange.

[00182] The excipients used in the capsule formulation are: microcrystalline cellulose, croscarmellose sodium, magnesium stearate (vegetable origin), and gelatin capsule shells. The capsule shells are comprised of gelatin, red iron oxide, and titanium dioxide. All excipients meet EP/USP/NF specifications.

[00183] Matched placebo capsules (placebo for Compound 1 hydrochloride capsules) contain the same excipients. In the placebo formulation, the hydrochloride of Compound 1 is replaced with microcrystalline cellulose.

[00184] Stability studies have indicated that such Compound 1 hydrochloride capsules are stable for up to 2 months at 40 °C/75% relative humidity accelerated storage conditions. Further stability studies have indicated that such Compound 1 hydrochloride capsules are stable for up to 6 months at 40 °C/75% relative humidity accelerated storage conditions.

Stability studies in the bulk container (30 ct/45 cc bottle) at long-term and accelerated storage conditions are run concurrently with a Phase I trial.

[00185] Stability studies of the matched placebo capsules at long-term and accelerated storage conditions are also run concurrently with a Phase I trial.

Example 6. A Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the hydrochloride salt of Compound 1.

[00186] *General Design and Methodology:* The purpose of this study is to assess the initial safety, tolerability, pharmacokinetics, and pharmacodynamics of Compound 1 (administered as Capsules of the hydrochloride salt of Compound 1) in healthy adults. In Part 1 of the study, individual subjects are administered single oral doses of the hydrochloride salt of Compound 1 (or matching placebo) in up to 4 treatment periods. In Part 2 of the study, individual subjects are administered daily oral doses of the hydrochloride salt of Compound 1 (or matching placebo) for up to 14 days. Data from this study is used to select doses and dose regimens for subsequent clinical studies.

[00187] This is a randomized, double-blind, placebo-controlled study to investigate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of ascending single oral doses (Part 1, Panels A and B) and of ascending multiple daily oral doses (Part 2, Panels C-G) of the hydrochloride salt of Compound 1 in healthy adult subjects.

[00188] In Part 1, Panels A and B consist each of eight healthy male adult subjects (randomized to receive single ascending doses of either the hydrochloride salt of Compound 1 or matching placebo in a 3:1 ratio, respectively) in up to 4 treatment periods (Periods 1 to 4), conducted in an alternating fashion. The effect of a high-fat breakfast on the pharmacokinetics of the hydrochloride salt of Compound 1 is assessed in Panel A.

[00189] In Part 2, Panels C through G consist each of eight healthy adult subjects (randomized to receive either the hydrochloride salt of Compound 1 or matching placebo in a 3:1 ratio, respectively) once a day for up to 14 days. In Part 2, Panels are dosed sequentially.

[00190] Since this is a Phase 1 assessment of the hydrochloride salt of Compound 1 in humans, and given that pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being evaluated, this protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical trials.

[00191] *Objectives:*

[00192] *Part I, Primary objective:* To evaluate the safety and tolerability of Compound 1 after administration of single ascending oral doses of the hydrochloride salt of Compound 1 to healthy male adult subjects.

[00193] *Part I, Secondary objective:* (1) To obtain preliminary plasma pharmacokinetics (*e.g.*, $C_{\max}$, $T_{\max}$, AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$) of the hydrochloride salt of Compound 1 following administration of single ascending oral doses to healthy male adult subjects. Hypothesis: At one or more well-tolerated single oral dose(s) of the hydrochloride salt of Compound 1, the geometric mean $AUC_{0-\infty}$ of Compound 1 is at least $0.4 \mu M \cdot hr$. (2) To compare the effects of a high-fat breakfast on the plasma pharmacokinetics of the hydrochloride salt of Compound 1 following administration of single ascending oral doses to healthy male adult subjects to those in the fasted state. Estimation: The effect of a standardized high-fat breakfast on the plasma pharmacokinetics (*e.g.*, $C_{\max}$, $T_{\max}$, $AUC_{0-\infty}$) of the hydrochloride salt of Compound 1 after oral administration of a single dose of the hydrochloride salt of Compound 1 to healthy male adult subjects are estimated. (3) To obtain preliminary data on urinary excretion of intact drug following administration of single ascending oral doses of the hydrochloride salt of Compound 1 to healthy male adult subjects.

[00194] *Part 2, Primary Objective:* To evaluate the safety and tolerability of the hydrochloride salt of Compound 1 administered as multiple daily oral doses for up to 14 consecutive days to healthy adult subjects.

[00195] *Part 2, Secondary Objective:* (1) To assess the single-dose and steady-state time-plasma concentration profile, and pharmacokinetic parameter values (*e.g.*, $C_{\max}$, $T_{\max}$, AUC_{0-24h} , $AUC_{0-\tau}$, $t_{1/2}$, accumulation ratio) of the hydrochloride salt of Compound 1 following administration of multiple daily oral doses of the hydrochloride salt of Compound 1 for up to 14 consecutive days to healthy adult subjects. Hypothesis: At one or more well-tolerated daily oral dose(s) of the hydrochloride salt of Compound 1, the steady-state geometric mean AUC_{0-24h} of Compound 1 is at least $0.4 \mu M \cdot hr$. (2) (If measured) To obtain preliminary data on urinary excretion of intact drug following administration of multiple daily oral doses of the hydrochloride salt of Compound 1 to healthy adult subjects.

[00196] *Number of subjects (planned):*

[00197] *Part 1:* Sixteen healthy adult male subjects between the ages of 18 and 55 years are enrolled in Part 1 of the study. Eight different subjects (randomized to receive hydrochloride salt of Compound 1 or matching placebo) participate in each panel of the study (Panels A and B).

[00198] Part 2: Up to forty healthy adult subjects (males, or females of non-childbearing potential) between the ages of 18 and 55 years are enrolled in Part 2 of the study. Eight different subjects (randomized to receive hydrochloride salt of Compound 1 or matching placebo) participate in each panel of the study (Panels C through G).

[00199] *Criteria for inclusion:*

[00200] A) Subject understands the study procedures and agrees to participate in the study by giving written informed consent.

[00201] B) Part 1: Subject is male, 18 to 55 years of age at the pre-study/screening visit.

[00202] C) Part 2: Subject is male, or female (not of reproductive potential) 18 to 55 years of age at the pre-study/screening visit; further:

(1) If subject is a postmenopausal female: subject is without menses for at least 1 year and has a documented follicle stimulating hormone (FSH) level in the postmenopausal range at pretrial (screening).

(2) If subject is a surgically sterile female: subject is status post hysterectomy, bilateral oophorectomy, or tubal ligation. (Hysterectomy may be confirmed by ultrasound or other imaging technique if documentation is not available. Oophorectomy and tubal ligation must be confirmed by documentation).

[00203] D) Subject has a Body Mass Index (BMI) > 18 to $\leq 30 \text{ kg/m}^2$ at the pre-study/screening visit. $\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$ (BMI calculation should be rounded to the nearest whole number).

[00204] E) Subject is judged to be in good health based on medical history, physical examination, and vital sign measurements, and laboratory safety tests obtained at pre-study/screening, and within 24 hours prior to first administration of study drug.

[00205] F) Subject has no clinically significant abnormality of electrocardiography (ECG) performed at pre-study/screening, and prior to first administration of study drug.

[00206] G) Subject is a nonsmoker and/or has not used nicotine or nicotine-containing products (*e.g.*, nicotine patch) for at least approximately 3 months.

[00207] H) Subject is willing to comply with the study restrictions.

[00208] I) Part 1: Subject is willing to eat the protocol-specified high-fat breakfast.

[00209] *Criteria for exclusion:*

[00210] A) Subject is under the age of legal consent.

[00211] B) Subject has a personal history of a clinically significant psychiatric disorder (including severe affective disorder, psychotic tendencies and drug-induced psychoses).

Subjects who have had situational depression or anxiety in the past may be enrolled at the discretion of the investigator.

[00212] C) Subject has a first-degree family history of schizophrenia, major affective disorder, or other psychosis.

[00213] D) Subject is mentally or legally incapacitated, has significant emotional problems at the time of pre-study/screening visit or is expected to have potential for mental incapacitation during the conduct of the study.

[00214] E) Subject has a history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by virtue of their participation in the study.

[00215] F) Subject has an estimated creatinine clearance (CrCl) of ≤ 80 mL/min based on the Cockcroft-Gault equation. An actual creatinine clearance, as measured using a 24-hour urine collection, may be used in place of, or in conjunction with the Cockcroft-Gault calculation. Subjects with an actual or calculated creatinine clearance that is in the range of 72-79 mL/min (*i.e.*, within 10% of 80 mL/min) may be enrolled in the study at the discretion of the investigator.

Cockcroft-Gault Equation:

$$\text{CrCl} = (140 - \text{age [yr]}) * (\text{body weight [kg]}) / (72 * \text{serum creatinine [mg/dL]})$$

Note: For female subjects, multiply by 0.85 to obtain creatinine clearance.

[00216] G) Subject has a history of stroke, chronic seizures, or major neurological disorder.

[00217] H) Subject has a history of clinically significant endocrine, gastrointestinal, cardiovascular, peripheral vascular, hematological, hepatic, immunological, renal, respiratory, or genitourinary abnormalities or diseases. Subjects with a history of uncomplicated kidney stones (defined as spontaneous passage and no recurrence in the last 5 years), or childhood asthma may be enrolled in the trial at the discretion of the investigator.

[00218] I) Subject has a history of clinically significant neoplastic disease, with the exception of adequately treated localized or in situ non-melanoma carcinoma of the skin (*i.e.*, basal cell carcinoma) or the cervix.

[00219] J) Subject has a history of significant multiple and/or severe allergies (*e.g.*, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerance to prescription or non-prescription drugs (including marijuana or other cannabis-containing drugs) or food.

[00220] K) Subject has had major surgery, donated or lost 1 unit (approximately 500 mL) of blood, or has participated in another investigational trial within 4 weeks prior to the pre-study/screening visit. The 4 week window is derived from the date of the last trial medication and / or blood collection in a previous trial and/or adverse event (AE) related to trial drug to the pretrial/screening visit of the current trial. For subjects who have participated in an investigational trial where no trial drug was administered or invasive procedure performed the interval may be revised to include no interval requirement.

[00221] L) Subject has had (within 8 weeks of pre-study/screening visit) or plans to have a preventive vaccination during the course of the study (*i.e.*, up to the post-study visit).

[00222] M) Subject is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies (such as St. John's Wort [*Hypericum perforatum*]) beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), until the post-study visit. There may be certain medications that are permitted.

[00223] N) Subject consumes excessive amounts of alcohol, defined as >3 servings of alcoholic beverages per day (1 serving is approximately equivalent to: 300 mL [10 ounces] of beer, 125 mL [4 ounces] of wine, 25 mL [1 ounce] of distilled spirits). Subjects that consume no more than 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.

[00224] O) Subject consumes excessive amounts of caffeine, defined as >6 servings of coffee, tea, cola, or other caffeinated beverages per day (1 serving is approximately equivalent to 120 mg of caffeine).

[00225] P) Subject is currently (defined as within approximately 3 months of the pre-study/screening visit) a regular user (including "recreational use") of any illicit drugs (including marijuana) or has a history of drug (including alcohol) abuse within approximately 6 months of the pre-study/screening visit.

[00226] Q) For male subjects: Subject is unwilling or unable to use a condom with female sexual partners from the time of first administration of study drug through three months after the final dose of study drug.

[00227] R) For male subjects: Subject is unwilling to refrain from sperm donation from the time of first administration of study drug through three months after the final dose of study drug.

[00228] S) Subject has a family history of long QT syndrome.

[00229] T) Subject has a QTc interval of > 450 msec (based on mean of triplicate ECGs obtained at baseline).

[00230] U) The investigator has concerns regarding the safe participation of the subject in the study or for any other reason the investigator considers the subject inappropriate for participation in the study.

[00231] *Investigational product, dosage and mode of administration:* Investigational drug product, hydrochloride salt of Compound 1, Capsules and matching placebo are supplied to the clinical research unit as formulated dry powder 2-, 10-, and 50-mg (free base equivalents) capsules for oral administration. Study drug is provided to the clinic site in appropriately labeled bulk packaging. An unblinded pharmacist (or designee under the direct supervision of the unblinded pharmacist) at the clinical site, who is otherwise not connected with the conduct of the study, dispenses blinded study drug for administration to subjects according to the provided allocation schedule. For Part 2, study drug to support dosing of individual subjects for up to the entire dosing duration (*i.e.*, 14 days) may be repackaged at the clinical site by the unblinded pharmacist (or designee under the direct supervision of the unblinded pharmacist). These repackaged blinded clinical supplies are administered to subjects at the clinical site only.

[00232] *Duration of treatment:*

[00233] Part 1: In Part 1, total study participation is approximately 84 days (including a 28 day screening period). There is a minimum washout period of at least 7 days between treatments in Part 1.

[00234] Part 2: In Part 2, total study participation is approximately 56 days (including a 28 day of screening period).

[00235] *Reference therapy, dosage and mode of administration:*

[00236] Part 1: In Panels A and B, each subject receives single ascending oral doses of the hydrochloride salt of Compound 1 or matching placebo in up to 4 treatment periods separated by a minimum 1-week washout interval between doses. There is a minimum 72-hour period between administration of study drug in Panels A and B. In addition, there is a minimum 2-week washout between Panel B Period 2 and Panel A Period 3 in order to evaluate available preliminary pharmacokinetic data along with safety and tolerability data from the preceding doses before proceeding with dosing in Periods 3 and 4. All doses are administered orally, together with approximately 240 mL of water. Water is otherwise restricted from 1 hour prior to, and for 1 hour after administration of study drug. In each

treatment period, with the exception of Panel A Period 4 (food effect treatment period); study drug is administered after an overnight fast (for approximately 8 hours).

[00237] Panel A: Subjects receive single 2-, 18-, 100- and 18-mg (with food) doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2) in Periods 1 through 4. The allocation schedule for Periods 2 and 4 (fasted versus fed) are the same such that the same subjects receive active drug or matching placebo in the respective treatment periods.

[00238] In Panel A Period 4, study drug are administered after consumption of a high-fat breakfast. The composition of the high-fat breakfast is: 2 fried or scrambled eggs, 2 strips bacon, 2 slices toast with 2 pats butter, 4 oz (113 gram) hash browns (fried potato), 240 mL whole milk (nutritional content approximately 55.6 gram fat, 55 gram carbohydrate, 31.1 gram protein ; total calories = 500.4 as fat, 220 as carbohydrate, 124.4 as protein). In this food-effect treatment period, subjects also fast from all food and drink, except water, for approximately 8 hours prior to study drug administration. However, approximately 30-minutes prior to study drug administration, subjects begin to consume the high-fat breakfast as described above. This meal should be consumed in its entirety over a 20-minute duration. Approximately 10 minutes after consuming the meal, subjects are administered their dose of study drug with approximately 240 mL water, and water is otherwise restricted for a further 1 hour after study drug administration.

[00239] Panel B: Subjects receive single 6-, 50-, 200-, and 400-mg doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2) in Periods 1 through 4.

[00240] The suggested doses of the hydrochloride salt of Compound 1 for dose escalation in Part 1 (Panels A and B) are provided in Table 2.

Table 2.

Panel: ^{a),b),c)}	Period 1	Period 2	Period 3	Period 4
Panel A	2 mg	18 mg ^{d)}	100 mg	18 mg (fed) ^{e)}
Panel B	6 mg	50 mg	200 mg	400 mg

^{a)} Subjects are randomized to receive single oral doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2).

^{b)} Different subjects participate in each panel.

^{c)} The stated doses can be adjusted downwards based on evaluation of safety, tolerability, and/or pharmacokinetic data from previous panels or treatment periods.

^{d)} For Panel A subjects, the assigned treatment in Period 4 are identical to that in Period 2 such that the same subjects receive placebo in these two treatment periods.

^{e)} Hydrochloride salt of Compound 1 to be administered with high-fat breakfast; dose of the hydrochloride salt of Compound 1 is repeated per subject based on the dose received in Period 2.

[00241] Note that the doses proposed here may be adjusted downwards based on preliminary pharmacokinetic, safety and tolerability data from preceding Panels or Periods.

[00242] Preliminary pharmacokinetic data from subjects in this study guide dose escalation to the higher doses. A pharmacokinetic pause occurs after Period 2 in Panel B, in order to assess available pharmacokinetic data along with safety and tolerability data prior to further dose escalation in Period 3 in Panel A. The planned doses may be adjusted downward based on evaluation of safety, tolerability, and /or pharmacokinetic data from previous panels or treatment periods.

[00243] Part 2: In Panels C through G, each subject receives daily oral doses of the hydrochloride salt of Compound 1 or matching placebo for up to 14 days. All doses are administered orally, together with approximately 240 mL of water. Water is otherwise restricted from 1 hour prior to, and for 1 hour after administration of study drug. Part 2 only initiates once preliminary pharmacokinetic, safety and tolerability data are available from Part 1 Panel A Period 3 (100 mg dose). Prior to dosing in the first Panel in Part 2 (*i.e.*, Panel C), a dose selection memo/interim report is provided to the Investigator and to the Ethics Review Committee (ERC)/Institutional Review Board (IRB). Dosing in Panel C does not proceed until the Investigator has received approval of the dose selected for Panel C from the ERC/IRB. Panels are conducted sequentially: dosing in a subsequent Panel only commences after preliminary evaluation of safety and tolerability data from the dosing phase of the preceding Panel has been evaluated (no less than one week between the first dose in Panels D, E, F, and G and the final dose in Panels C, D, E, and F respectively). In each treatment period, study drug is administered after an overnight fast (for approximately 8 hours).

[00244] Panel C: Subjects receive daily oral 10-mg doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2) for up to 14 days.

[00245] Panel D: Subjects receive daily oral 20-mg doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2) for up to 14 days.

[00246] Panel E: Subjects receive daily oral 40-mg doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2) for up to 14 days.

[00247] Panel F: Subjects receive daily oral 80-mg doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2) for up to 14 days.

[00248] Panel G: Subjects receive daily oral 160-mg doses of the hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2) for up to 14 days.

[00249] Note that the doses proposed here may be adjusted downwards based on preliminary pharmacokinetic, safety and tolerability data from preceding Panels or Treatment Periods.

[00250] For all single-doses (*i.e.*, all doses in Part 1) and for the first (Day 1) and last (Day 14) doses administered in Part 2, all subjects fast for a minimum of approximately 4-hours post-dose (except for water, which is permitted starting 1 hour after dosing). A standardized lunch is administered approximately 4 hours post-dose, a standardized dinner at approximately 10 hours post-dose, and snacks may be offered at 7 and 13 hours post-dose. For the purposes of this study, “standardized” means that the caloric content and composition should be similar across treatment periods and panels. For non-dosing days (Part 1) and for non-dosing days and dosing days 2 through 13 (Part 2), meals do not need to be standardized.

[00251] The suggested doses of the hydrochloride salt of Compound 1 for dose escalation in Part 2 (Panels C through G) are provided in Table 3.

Table 3.

a),i),ii) Panel:	Panel C	Panel D	Panel E	Panel F	Panel G
Dose of hydrochloride salt of Compound 1	10 mg	20 mg	40 mg	80 mg	160 mg

a) Subject is randomized to receive single oral doses of hydrochloride salt of Compound 1 (n=6) or matching placebo (n=2).

i) Different subjects participate in each panel.

ii) The stated doses may be adjusted downwards based on evaluation of safety, tolerability, and/or pharmacokinetic data from previous panels or treatment periods.

[00252] *Criteria for evaluation:*

[00253] Pharmacokinetics/Pharmacodynamics:

- Blood and urine for determination of Compound 1 plasma and urine concentrations.

[00254] The urine is potentially analyzed for qualitative metabolite characterization.

[00255] In Part 1, urine samples for the determination of urinary Compound 1 concentrations are collected predose, and up to 48 hours post-dose in a selected treatment period in Part 1, as appropriate (at the highest expected dose (SAD), and in one treatment period only).

[00256] Urine samples are collected for up to 48 hours after the final dose of study drug on Day 14 of each treatment panel (in two collection aliquots: 0-24h and 24-48h). The decision to assay these urine samples for Compound 1 quantification and urinary excretion characterization, and potentially for qualitative metabolite characterization is made based on preliminary urinary PK data from Part 1. Based on these Part 1 urinary PK data, no, some, or all urine PK samples collected in Part 2 are assayed. In addition, based on preliminary

data, urine collection in later Panels may be discontinued. If necessary, and to increase the sensitivity of detection, urine samples from subjects in a given Panel may be pooled prior to analysis.

[00257] Safety: The safety and tolerability of the hydrochloride salt of Compound 1 is monitored by clinical assessment of adverse events and by repeated measurements of vital signs, physical examination, weight, neurological examinations, 12-lead electrocardiograms (ECGs), and by the standard clinical laboratory safety tests (hematology, chemistry, and urinalysis).

[00258] Adverse event inquiry occurs at 0 hour (pre-dose) and at each visit throughout the study, up to and including the post study visit (at least 14 days after the last dose of study drug).

[00259] *Statistical methods:*

[00260] Sample Size/Power: Sample size for initial human safety studies are limited and chosen based on customary values. Power calculations for comparison of adverse event rates are too imprecise to be clinically meaningful because the actual rates are not even approximately known. However, if an adverse event occurs at a rate of 1% or 10% then the probability of observing such an adverse event among the 6 subjects receiving that dose is 6% or 47%, respectively. If no AE of a given type is observed in any of the 6 subjects at a given dose then, with 80% (90%) confidence, the true incidence of the adverse event at that dose is at most 24% (32%).

[00261] Randomization: Subjects are randomized within a cohort according to a computer-generated random code.

[00262] Statistical Methods:

[00263] PK: Descriptive statistics are provided by treatment (Part 1) and by treatment and day (Part 2). Minimum, median, maximum and CV are provided for all PK parameters. Arithmetic mean and standard deviation based on the raw scale are provided for AUC and Cmax. In addition, the percent CV of AUC and Cmax is also provided and calculated according to the following formula: $100 \times \sqrt{\exp(s^2) - 1}$, where s^2 is the observed variance on the natural log-scale. Harmonic mean and jack-knife SD is provided for half-life. Time to steady-state, and evaluation of PK linearity are evaluated in an exploratory fashion.

[00264] Pharmacodynamics:

[00265] Part 1

[00266] Single-dose 2-AG concentrations and MGLL TE percentages are listed and summarized by time point and treatment using descriptive statistics. For each subject and each post-baseline time point, percent of baseline is calculated. Baseline is defined as the level in the last sample before test treatment of each period. Percent of baseline is computed via back-transformation from log-scale summary statistics. Other PD readouts may be summarized similarly.

[00267] Part 2

[00268] Multiple-dose 2-AG concentrations and MGLL TE percentages are listed and summarized by day and treatment using descriptive statistics. For each subject and each post-baseline time point, percent of baseline are computed via back-transformation from log-scale summary statistics. Other PD readouts may be summarized similarly.

[00269] *Part 1 (Single Ascending Dose, Panels A and B) Results*

[00270] Seventeen healthy male subjects had received at least one dose of study drug in Part 1. When administered in the fasting state, single oral doses up to 200 mg of Compound 1 HCl were not associated with any vital sign, safety laboratory, or electrocardiographic findings of note.

[00271] Compound 1 plasma concentrations were detectable at the 2-mg dose level, and increased with increasing dose. A summary of preliminary mean PK data is shown in Table 4. At the highest dose level administered (200 mg), mean C_{max} = 109 ng/mL, mean T_{max} = 3.0 hr, median $t_{1/2}$ = 3.61 hr, and mean AUC_{inf} = 766 ng•hr/mL.

Table 4.

Dose (mg)	C_{max} (ng/mL)*	SD C_{max}	T_{max} (hr)*	SD T_{max}	AUC_{inf} (hr•ng/mL)*	SD AUC_{inf}	$T_{1/2}$ (hr) [#]
2	2.90	1.15	1.50	0.54	15.9	5.18	1.51
6	10.2	5.33	1.67	0.51	47.0	7.83	2.23
18	23.5	14.7	2.00	1.1	109	75.2	3.02
50	59.8	19.5	1.80	0.44	296	121	3.44
100 (A3)	45.7	40.0	3.17	2.56	289	185	5.82
100 (B4)	76.0	41.7	1.83	0.40	512	355	3.76
200	109	62.9	3.00	2.45	766	383	3.61

*Mean; [#]Median; A3 = Panel A, Period 3; B4 = Panel B, Period 4; SD = Standard Deviation

[00272] As shown in Table 4, there was a difference in the mean and SD of plasma PK parameter values for the two treatment periods (Panel A, Period 3; Panel B, Period 4) in which the 100 mg dose was administered: the values for Period A3 were lower than those

for Period B4, and also were not consistent with the dose-related increases observed across all other doses administered in the fasted state in Part 1 of the study. As described below, the peripheral blood mononuclear cell (PBMC) MGLL target engagement (TE) data indicated similar TE in Periods A3 and B4, that was greater than, and distinct from that in Period B2 in which a 50 mg dose was administered. These data suggest that the plasma PK data for Period A3 are anomalous. An evaluation of the laboratory procedures associated with the bioanalysis of these PK samples did not reveal a cause for this apparent anomaly, and values for both treatment periods are reported here for completeness.

[00273] Peripheral Blood Mononuclear Cell (PBMC) aliquots were collected from subjects in order to evaluate in an exploratory fashion the dose- and time-dependence of Compound 1 mediated inhibition of MGLL, also referred to as MGLL target engagement (TE).

Preliminary data from selected treatment periods are shown in **Fig. 6** wherein the activity of MGLL is assayed in PBMC fractions by a hydrolysis assay in which exogenous 2-arachidonylglycerol (2-AG) is added to the PBMC pellet and the generation of arachidonic acid (AA) quantitated by mass spectroscopy. The hydrolytic activity at baseline (i.e., predose) is set at 100%. Inhibition of MGLL results in decreased hydrolysis of 2-AG in a time- and dose-dependent manner as indicated here. MGLL accounts for the majority of 2-AG hydrolysis under these conditions, however there is an MGLL-independent component, the magnitude of which is indicated on the graph by the maximal TE line, which represents the hydrolysis of 2-AG in PBMC pellets that have been pre-incubated with an excess of Compound 1.

[00274] As indicated in **Fig. 6** oral administration of Compound 1 HCl was associated with a time- and dose-dependent inhibition of MGLL hydrolytic activity. Following the 50 mg dose, mean maximal inhibition of MGLL activity occurred at approximately 2 hours postdose, whereas after the 100 mg and 200 mg doses, mean maximum inhibition occurred at approximately 4-8, and 8 hours respectively. The 200 mg dose of Compound 1 HCl was associated with complete inhibition of MGLL in PBMC at approximately 8 hours postdose, followed by a gradual return towards baseline activity. The 50 mg dose of Compound 1 HCl was associated with approximately 46% mean maximum reduction in total PBMC 2-AG hydrolytic activity, which corresponds to a mean-maximum MGLL-inhibition of approximately 54% after this dose.

[00275] *Part 2 (Multiple Ascending Dose, Panels C-D) Results*

[00276] There were no adverse events leading to the discontinuation of any subjects in Panel C (10 mg QD x 14 days) or Panel D (20 mg QD x 14 days) and no clinically significant changes in vital signs, laboratory test values, or ECGs.

[00277] For Panels C and D, the mean Compound 1 plasma PK profiles measured on days 1 and 13 of dosing are shown in **Fig. 7** and **Fig. 8** respectively. The preliminary PK data from these partial Panels, indicate Compound 1 plasma AUC_{0-24h} accumulation ratios (Day13/Day1) of ~1.2 and ~1.7, and plasma C_{max} accumulation ratios (Day13/Day1) of ~1.2 and ~1.2 for Panels C and D respectively. All daily doses of study drug in Part 2 were administered in the fasted state.

[00278] Preliminary biomarker (PBMC MGLL Target Engagement as measured by PBMC-mediated hydrolysis of 2-AG) data from the fourteen subjects who have completed dosing in Panels C and D (seven subjects in each of the two Panels) are shown with the relevant preliminary PBMC target engagement data for Placebo recipients (Panels C and D combined), Compound 1 HCl 10 mg QD (Panel C), and 20 mg QD (Panel D) in **Fig. 9**, **Fig. 10**, and **Fig. 11** respectively. These preliminary data from partially-completed Panels, suggest that after 14 days of Compound 1 HCl daily doses of 20 mg, MGLL in PBMC remains substantially inhibited at the end of the 24 hour dosing interval (**Fig. 11**). At the 10 mg QD dose, mean MGLL inhibition at the end of the dosing interval is similar on dosing Days 1 and 14, suggesting that MGLL hydrolytic activity is able to recover fully by 24 hours after dosing of Compound 1 HCl at 10 mg QD (**Fig. 10**).

Example 7. A Single-Dose, Randomized, Placebo Controlled, Two Period Crossover Study of the Effects of Compound 1 Hydrochloride Salt on Gastric Accommodation and Nutrient Volume Tolerance.

[00279] The primary objective of this study is to assess the effect of Compound 1 HCl on gastric accommodation in patients with functional dyspepsia (FD).

- Assess the effect of Compound 1 HCl on nutrient volume tolerance compared to placebo;
- Assess safety and tolerability of Compound 1 HCl in FD subjects;
- Assess changes in IGP, nutrient volume tolerance, satiety (Satiety Scale, Appendix F) and epigastric symptoms (VAS for Epigastric Symptoms, Appendix G) as related to Compound 1 HCl plasma concentrations (e.g., C_{max} , AUC_{0-4} , AUC_{0-24}) and monoacylglycerol lipase (MGLL) enzyme activity in peripheral blood mononuclear cells (PBMC).

[00280] Patients: Twelve adult male or female patients with functional dyspepsia, and with previously identified impaired gastric accommodation, between the ages of 18 and 65 years will be enrolled.

[00281] Criteria:

Inclusion Criteria:

- Patient has functional dyspepsia, defined by the Rome III criteria (Appendix E). The patient must have either the cardinal symptom of bothersome postprandial fullness or early satiation for the last 3 months, with symptom onset at least 6 months prior to screening and in the absence of organic, metabolic or systemic diseases that can explain these symptoms.
- Patient has, upon clinical review, evidence of impaired gastric accommodation based on a barostat test, a nutrient volume tolerance test with intragastric pressure measurement, or by other, similar evaluations. The evidence for this abnormality will be recorded.
- Patient's Rome III Questionnaire results indicates that the intensity of co-existing epigastric pain and/or epigastric burning may be present, but have the same or lesser intensity than the evaluations of postprandial fullness or early satiety (i.e. epigastric pain and burning are not the prominent symptoms of the patient's functional dyspepsia).
- Patient recall of symptoms of gastrointestinal reflux (e.g. heartburn, regurgitation) over the past 8 weeks has no more than 2 episodes per week of heartburn or regurgitation considered mild in intensity. (The Reflux Disease Questionnaire (RDQ) will collect these symptoms)
- Patient is willing to discontinue specific drugs that affect gut motility for at least 2 weeks prior to each treatment period. Restricted drugs include opioids (e.g. loperamide), dopamine antagonists (e.g. metoclopramide, domperidone, alizapride), other prokinetic agents (e.g. cispride, tegaserod), acid secretion (e.g. H₂ antagonists and proton pump inhibitors such as omeprazole, esomeprazole, lansoprazol, pantoprazol), and erythromycin.
- Patient understands the study procedures and agrees to participate in the study by giving written informed consent.
- Patient is a male or female between 18 and 65 years of age at the pre-study/screening visit; further:
 - If subject is a male, he is willing to use a condom with female sexual partners from the time of first administration of study medication and for 3 months following the last dose of study medication.
 - Subject is willing to refrain from sperm donation from the time of first administration of study medication and for 3 months following the last dose of study medication.
 - If subject is a postmenopausal female: subject is without menses for at least 1 year and has a documented follicle stimulating hormone (FSH) level in the postmenopausal range at the pre-study/screening visit.
 - If subject is a surgically sterile female: subject is status-post hysterectomy, bilateral oophorectomy, or tubal ligation. (Hysterectomy may be confirmed by ultrasound or other

imaging technique if documentation is not available. Oophorectomy and tubal ligation must be confirmed by documentation).

- If subject is a woman of child bearing potential (WOCBP), she agrees to use two methods of barrier contraception which may include cervical cap with spermicide, diaphragm with spermicide, condom with spermicide, or intrauterine device (IUD) from time of screening through the last study visit. In addition, WOCBP will have a negative urine pregnancy test at screening and before being dosed with study medication. WOCBP who are using injectable contraceptives, implanted contraceptives, medicated ring contraceptives or oral contraceptive methods may participate, but must use one method of barrier contraception such as cervical cap with spermicide, diaphragm with spermicide, or condom with spermicide.
- **Patient has a Body Mass Index (BMI) >18 to ≤ 30 kg/m²** at the pre-study/screening visit.
- **BMI = weight (kg)/height (m)²** (BMI calculation should be rounded to the nearest whole number).
- Patient is judged to have no unmanaged significant disease or disorder based on medical history, physical examination, vital sign measurements, and laboratory safety tests (see Appendix B for interpretation of laboratory findings) obtained at pre-study/screening, and within 24 hours prior to first administration of study drug.
- Patient has no clinically significant abnormality of ECG performed at pre study/screening, and prior to first administration of study drug.
- Patient is a nonsmoker or is a social smoker using no more than 2 cigarettes per day, and is willing to abstain from smoking and nicotine containing products before reporting to the clinical research unit until discharge at the completion of study procedures.
- Patient is willing to comply with the study restrictions.
- Patient is willing to undergo the nutrient volume tolerance tests.

Exclusion Criteria:

- Patient is under the age of legal consent.
- Female patients who are pregnant or breastfeeding.
- Patient has a personal history of a clinically significant psychiatric disorder (including severe affective disorder, anxiety disorder, post-traumatic stress disorder, psychotic disorder or drug-induced psychoses). Patients who have had adjustment disorder with anxious or depressive features in the past may be enrolled at the discretion of the Investigator.
- Patient has a first-degree family history of schizophrenia, severe affective disorder, severe anxiety disorder, or other psychosis.
- Patient is taking antidepressants including SSRIs, SNRIs, tricyclic antidepressants, or atypical antidepressant medications such as bupropion, mirtazapine, trazodone or agomelatine. Patients taking these or other types of medicine for anxiety are also excluded.

Patients who have discontinued antidepressants more than 6 months ago may be enrolled at the discretion of the Investigator. Patients who are taking gabapentin or pregabalin or buspirone are also excluded.

- Patient is mentally or legally incapacitated, has significant emotional problems at the time of pre-study/screening visit or is expected to have potential for mental incapacitation during the conduct of the study.
- Patient has a history of any illness that, in the opinion of the study Investigator, might confound the results of the study or pose an additional risk to the subject by virtue of their participation in the study.
- Patient has had any gastrointestinal surgery. Those having undergone appendectomy more than 1 year prior to the pre-study/screening visit may participate.
- Patient has had any acute gastrointestinal illness in the past 3 months.
- **Patient has an estimated creatinine clearance (CrCl) of ≤ 80 mL/min based on the Cockcroft-Gault equation.** An actual creatinine clearance, as measured using a 24-hour urine collection, may be used in place of, or in conjunction with the Cockcroft-Gault calculation. Subjects with an actual or calculated creatinine clearance that is in the range of 72-79 mL/min (i.e., within 10% of 80 mL/min) may be enrolled in the study at the discretion of the Investigator.

Cockcroft-Gault Equation:

$$\text{CrCl} = (140 - \text{age [yr]}) * (\text{body weight [kg]}) / (72 \text{ serum creatinine [mg/dL]})$$

For female subjects, multiply by 0.85 to obtain creatinine clearance

- Subject has an active or prior history of neurological disorder, including but not limited to seizure disorder, epilepsy, stroke, neurological disease, cognitive impairment, head trauma with prolonged loss of consciousness (>10 minutes), or migraine headaches.
- Patient is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies (such as St. John's Wort [Hypericum perforatum]) beginning approximately 1 week prior to administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), until the second treatment period. There may be certain medications that are permitted.
- Patient has a history of clinically significant neoplastic disease, with the exception of adequately treated localized or in situ non-melanoma carcinoma of the skin (e.g., basal cell carcinoma) or the cervix.

- Patient has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs (including marijuana or other cannabis-containing drugs) or food.
- Patient has had major surgery, donated or lost 1 unit (approximately 500 mL) of blood, or has participated in another investigational trial within 4 weeks prior to the pre-study/screening visit. The 4 week window will be derived from the date of the last trial medication and / or blood collection in a previous trial and/or adverse event (AE) related to trial drug to the pretrial/screening visit of the current trial. For patients who have participated in an investigational trial where no trial drug was administered or invasive procedure performed the interval may be revised to include no interval requirement.
- Patient has had (within 8 weeks of pre-study/screening visit) or plans to have a preventive vaccination during the course of the study (e.g., up to the post-study visit).
- Patient consumes excessive amounts of alcohol, defined as >3 servings of alcoholic beverages per day (1 serving is approximately equivalent to: 300 mL [10 ounces] of beer, 125 mL [4 ounces] of wine, 25 mL [1 ounce] of distilled spirits). Subjects that consume no more than 4 servings of alcoholic beverages per day may be enrolled at the discretion of the Investigator.
- Patient consumes excessive amounts of caffeine, defined as >6 servings of coffee, tea, cola, or other caffeinated beverages per day (1 serving is approximately equivalent to 120 mg of caffeine).
- Patient is currently (defined as within approximately 3 months of the pre-study/screening visit) a regular user (including “recreational use”) of any illicit drugs (including marijuana) or has a history of drug (including alcohol) abuse within approximately 6 months of the pre-study/screening visit. Further, patient is unwilling to refrain from the use of cannabis products during this study.
- Subject has a family history of long QT syndrome.
- Subject has a QTc interval of >450 msec (male subjects) or >470 msec (female subjects).
- The Investigator has concerns regarding the safe participation of the patient in the study or for any other reason the Investigator considers the subject inappropriate for participation in the study.

[00282] Subjects/patients will be randomized to a crossover treatment sequence A or B according to a computer-generated random code.

Period 1	Period 2
Sequence A: Placebo	Compound 1 HCl
Sequence B: Compound 1 HCl	Placebo

Blinding: Compound 1 HCl or matching placebo will be prepared using the randomization allocation schedule by an unblinded pharmacist without other responsibilities for the collection of safety or efficacy data.

[00283] Duration of Treatment: Total study participation will be approximately 83 days, including a 60 day screening period. There will be a minimum washout period of at least 7 days between two single day treatments. Efforts should be made to complete the second treatment within 4 weeks of the first treatment. WOCBP not using hormonal contraception should be studied at each of the two treatment periods at the same point in their menstrual cycle.

[00284] The primary endpoint is the change in IGP over time during nutrient meal infusion (gastric accommodation) comparing Compound 1 versus placebo. For each subject this is computed from the area between the pressure time curve and the zero line (with values above zero contributing negatively) from the beginning of the nutrient drink infusion until it ceases.

[00285] Other endpoints include the Satiation Score and VAS for Epigastric Symptoms measured over time during the nutrient volume tolerance test, and in the period after the nutrient volume tolerance test until the pressure transducer is removed.

Example 8: Phase 2 Single Site, Randomized, Double-blind, Placebo Controlled Trial of Compound 1 in Subjects With Alzheimer's Disease

[00286] The purpose of this study is to evaluate the safety and efficacy of Compound 1 HCl in the treatment of Alzheimer's Disease.

[00287] Patients: Eligible subjects will be men and women 40 years to 95 years of age.

[00288] Criteria:

Inclusion Criteria:

- NINCDS/ADRDA criteria for probable AD
- MMSE between 12-27
- Treatment with a cholinesterase inhibitor or an NMDA (N-methyl-D-aspartate) antagonist with stable dose for at least 12 weeks
- Home monitoring available for supervision of medications
- Caregiver available to accompany patient to all visits and willing to participate in study as informant
- Fluent in English or Spanish

- Medical stability for this study as confirmed by review of records, internist's physical exam, neurological exam, and laboratory tests
- Stable doses of non-excluded medication
- No evidence of hepatic insufficiency
- Able to swallow oral medications
- Ability to participate in the informed consent process

Exclusion Criteria:

- History of Diabetes Mellitus (OGTT criteria) requiring treatment with an excluded antidiabetic medication (see below) or history of hypoglycemia
- Active hepatic or renal disease
- Cardiac disease including history of congestive heart failure or current treatment for CHF; history of recent myocardial infarction
- Use of another investigational drug within the past two months
- History of clinically significant stroke
- History of seizure or head trauma with disturbance of consciousness within the past two years
- Major mental illness including psychotic disorders, bipolar disorder, or major depressive episode within the past two years
- Medication Exclusion
- Current use of oral hypoglycemic agents including sulfonylureas and meglitinides
- Current or past treatment with insulin for longer than two weeks
- Current use of drugs with significant anticholinergic or antihistaminic properties

[00289] Study Design:

- Allocation: Randomized
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Change in Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) Score [Time Frame: Over 6 months, measured at visits 2 (week 2), 6 (week 12), 8 (week 24)] [

Designated as safety issue: No]

- A psychometric instrument that evaluates memory, attention, reasoning, language, orientation, and praxis.

Secondary Outcome Measures:

- Change in Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change (ADCS-CCGIC) Score [Time Frame: Over 6 months, measured at visits 2 (week 2), 6 (week

12), 8 (week 24)] [Designated as safety issue: No]. A systematic method for assessing clinically significant change in a clinical trial as viewed by an independent skilled and experienced clinician . The ADCS-CGIC focuses on clinician's observations of change in the subject's cognitive, functional, and behavioral performance since the beginning of a trial. It relies on both direct examination of the subject and an interview of an informant. Unlike a targeted symptom scale, it takes into account a subject's overall function in the cognitive, behavioral, and functional activity domains.

- Change in Mini-Mental State Examination (MMSE) Score [Time Frame: Over 6 months, measured at visits 2 (week 2), 6 (week 12), 8 (week 24)] [Designated as safety issue: No]. A frequently used screening instrument for Alzheimer's disease drug studies. It evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two intersecting polygons.
- Change in Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) Score [Time Frame: Over 6 months, measured at visits 2 (week 2), 6 (week 12), 8 (week 24)] [Designated as safety issue: No]. ADCS-ADL assesses functional performance in subjects with Alzheimer's disease. In a structured interview format, informants are queried as to whether subjects attempted each item in the inventory during the prior 4 weeks and their level of performance. The ADCS-ADL scale discriminates well between normal controls and mild AD patients. It has good test-retest reliability. The ADCS-ADL includes some items from traditional basic ADL scales (e.g., grooming, dressing, walking, bathing, feeding, toileting) as well as items from instrumental activities of daily living scales (e.g., shopping, preparing meals, using household appliances, keeping appointments, reading).
- Change in Neuropsychiatric Inventory (NPI) Score [Time Frame: Over 6 months, measured at visits 2 (week 2), 6 (week 12), 8 (week 24)] [Designated as safety issue: No]. The NPI is a well-validated, reliable, multi-item instrument to assess psychopathology and behavior in AD based on interview with the informant.
- Changes in AD Biomarkers [Time Frame: Blood collected at visits 2 (week 2), 6 (week 12), 8 (week 24)] [Designated as safety issue: No]. Plasma beta-amyloid proteins will be collected from blood samples obtained at visit 2 (week 2), visit 6 (week 12), and visit 8 (week 24).
- APO-E genotyping [Time Frame: Collected at visit 2 (week 2)] [Designated as safety issue: No] APOe e4 is an important genetic risk factor for AD. In this trial, as in many studies of AD and memory and cognition in aging, the APOe e4 allele will be analyzed as a predictor of clinical change over time.

Arms	Assigned Interventions
Experimental: Compound 1 HCl Subjects with Alzheimer's Disease Intervention: Drug: Compound 1 HCl	Drug: Drug: Compound 1 HCl A natural product, found in many foods and plants with mild insulin sensitizing effects
Placebo Comparator: Placebo Subjects with Alzheimer's Disease Intervention: Drug: Placebo	Drug: Placebo Subjects with Alzheimer's Disease placebo comparator

Example 9: Investigation of Compound 1 HCl in Patients With Functional Chest Pain

[00290] About 200,000 new cases of Functional Chest Pain (FCP) are diagnosed annually in USA. FCP is associated with poor quality of life and high health care expenditure.

Gastroesophageal reflux disease (GERD), esophageal motility disorders, and psychological disorders may cause FCP. However, the mechanism(s) for FCP continue to be explored and include central and peripheral hypersensitivity as well as biomechanical dysfunction of the esophageal wall. CB1 receptor activation in synaptic clefts fine tunes neuronal firing and may in fact quell the over excitation associated with hypersensitivity. The purpose of this study is to evaluate the safety and efficacy of Compound 1 HCl in the treatment of Functional Chest Pain.

[00291] Patients: Eligible subjects will be men and women 18 years to 75 years of age.

[00292] Criteria:

Inclusion Criteria:

- At least one episode of chest pain a week in the past month. Previous negative cardiac evaluation (EKG ± non invasive stress test ± coronary angiogram). Negative esophageal evaluation for a motility disorder (eg: achalasia) and GERD (normal endoscopy, normal 24 hr pH study, or unresponsive to 6 weeks of BID PPI therapy)

Exclusion Criteria:

- Subjects requiring narcotics or other pain medications
- Subjects with known GERD (unless responsive to PPI therapy and on a stable dose), esophagitis, Barrett's esophagus or peptic stricture on endoscopy
- Subjects with previous upper gastrointestinal surgery
- Pregnancy

- Subjects with diabetes, neuromuscular disorders, cardiac disorders, or other severe co-morbidities (Cardiovascular, respiratory, renal, hepatic, hematologic, endocrine, neurologic) History of seizure or head trauma with disturbance of consciousness within the past two years
- Subjects with upper airway symptoms (such as hoarseness, wheezing or laryngospasm)
- Medications such as baclofen, sucralfate and prokinetic agents or any agent considered a sedative, hypnotic, or psychoactive drug
- Known history of substance abuse
- Subject unable to consent
- Patient has history of comorbid psychiatric conditions including mania and schizophrenia. Patients will also be excluded who currently have a diagnosis of depression or undergoing treatment for depression

[00293] Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Chest Pain [Time Frame: Daily assessment for 12 weeks]

[Designated as safety issue: No]. Patient will fill out a Chest Pain Questionnaire and symptom diary daily of symptoms which will be normalized to a numerical value for comparison among groups

Secondary Outcome Measures:

- Chest Pain Intensity [Time Frame: Daily assessment for 12 weeks]

[Designated as safety issue: No]. Patient will fill out a Chest Pain Questionnaire and symptom diary daily of symptoms which will be normalized to a numerical value for comparison among groups.

- GERD Symptom Checklist [Time Frame: Baseline, 2, 4, 8, and 12 weeks]

[Designated as safety issue: No] [Time Frame: Over 6 months, measured at visits 2 (week 2), 6 (week 12), 8 (week 24)] [Designated as safety issue: No]. Patients will fill out a questionnaire pertaining to GERD symptoms which will be normalized to a numerical value for comparison among groups.

- Short Form 36 [Time Frame: Baseline, 2, 4, 8, and 12 weeks]

[Designated as safety issue: No]

A general health-related quality of life questionnaire that examines 8 domains: Physical Functioning, Role Functioning Physical, Role Functioning Emotional, Mental Health, Vitality, Bodily Pain, General Health, and Social Functioning.

- Esophageal Hypersensitivity and Distention [Time Frame: Baseline, 4, 8, and 12 weeks] [Designated as safety issue: No]. Sensory thresholds for first sensation, discomfort, and pain in the esophagus. Frequency, amplitude, area under the curve (AUC) of reactive esophageal contractions.

Arms	Assigned Interventions
Experimental: Compound 1 HCl Patients who receive Compound 1 HCl, every other night, orally	Drug: Compound 1 HCl Compound 1 HCl, every other night, orally
Placebo Comparator: Placebo Patients who receive placebo, every other night, orally	Drug: Placebo Placebo--no drug

Example 10: Phase 3 Clinical Study of Compound 1 HCl for Multiple Sclerosis Pain and Spasticity

[00294] The purpose of this study study is to assess the efficacy and safety of Compound 1 HCl compared with placebo on the reduction of pain severity in participants with central neuropathic pain and moderate to severe spasticity due to Multiple Sclerosis.

[00295] Patients: Eligible subjects will be men and women 18 years to 75 years of age.

[00296] Criteria:

Inclusion Criteria:

- Have central neuropathic pain due to multiple sclerosis (MS) based on the disease diagnostic criteria
 - Adult males or females
 - Have a score of 4 or greater on the daily 24-hour average pain score
 - Females must test negative for pregnancy at study entry
 - Complete the daily diaries for at least 70% of the days of the study
 - Participants may continue other prescription and nonprescription analgesic pain medications as long as the dose has been stable for 1 month prior to study entry, and they agree to maintain that stable dose throughout the study
- Disease Diagnostic Criteria:
- Diagnosis of MS at least 1 year prior to study entry

- No MS flares or change in disease treatment for the 3 months prior to study entry
- Daily pain due to MS for a minimum of 3 months prior to study entry

Exclusion Criteria:

- Are currently in a clinical trial of MS disease-modifying therapy
- Have pain that cannot be clearly differentiated from causes other than MS
- Any current or historical diagnosis of mania, bipolar disorder, psychosis, or schizoaffective disorder
- History of substance abuse or dependence
- Are pregnant or breast-feeding

Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Change From Baseline in the Weekly 24-Hour Average Pain Scores at Week 6 (Acute Phase) [Time Frame: Baseline, 6 weeks] [Designated as safety issue: No]. 24-hour average pain severity scores recorded daily on an 11-point Likert scale, evaluated as a weekly mean, with scores ranging from 0 (no pain) to 10 (worst possible pain). Participants should complete electronic diary each day upon awakening. The 11-point Likert scale was used for assessment of 24-hour average pain and evaluated as weekly means. Scores range from 0 (no pain) to 10 (worst possible pain). The Least Squares Mean (LS Mean) Value was adjusted for investigative site and baseline severity.
- Change From Baseline in Spasticity NRS score at Week 6 [Time Frame: Baseline, 6 weeks] [Designated as safety issue: No]. The spasticity Numeric Rating Scale is a 0 to 10 patient reported scale of spasticity severity, with 0 being no spasticity and 10 being worst possible spasticity.

Secondary Outcome Measures:

- Change From Baseline in the Weekly 24-Hour Average Pain Scores up to Week 6 (Acute Phase) [Time Frame: Baseline, 6 weeks] [Designated as safety issue: No]. This is a nominal outcome reflecting whether or not a clinically-important efficacy outcome ($\geq 30\%$ or $\geq 50\%$ pain reduction from baseline) was achieved at endpoint. It is based on a comparison between baseline and endpoint scores on an ordinal scale with scores from 0 (no pain) to 10 (worst

possible pain). Used were the weekly mean of the scores of the average pain severity over the last 24 hours. The weekly averages were based on daily assessments recorded by participants in their diaries.

- Change From Baseline in Ashworth Spasticity Score at Week 6 [Time Frame: 6 weeks] [Designated as safety issue: No]. The Ashworth spasticity score is a physician assessed rating of spasticity using a five point score from 0 to 4 for each muscle group tested.
- Patient Global Impressions of Improvement Scale (PGI-I) at 6 Weeks [Time Frame: 6 weeks] [Designated as safety issue: No]. A scale that measures the participant's perception of improvement at the time of assessment compared with the start of treatment. The score ranges from 1 (very much better) to 7 (very much worse). The Least Squares (LS) Mean Value was adjusted for investigative site and baseline severity.
- Change From Baseline in the Brief Pain Inventory Severity and Interference Scores (BPI-S/BPI-I) at Week 6 (Acute Phase) [Time Frame: Baseline, 6 weeks] [Designated as safety issue: No]. Measures pain severity and interference on function. Severity scores: 0 (no pain) to 10 (severe pain) on each question assessing worst, least, and average pain in past 24 hours, and pain right now. Interference scores: 0 (does not interfere) to 10 (completely interferes) on each question assessing pain interference in past 24 hours, such as general activity, mood, normal work, relations with other people, and sleep. Average interference=average of non-missing scores of individual interference items. Least Squares (LS) Mean Value was adjusted for investigative site and baseline severity.
- Change From Baseline in the Weekly Mean of Night Pain Scores at Week 6 (Acute Phase) [Time Frame: Baseline, 6 weeks] [Designated as safety issue: No]. Weekly mean of the night pain severity scores recorded daily on an 11-point Likert scale, an ordinal scale ranging from 0 (no pain) to 10 (worst possible pain). Participants should complete the electronic diary each day upon awakening. The Least Squares (LS) Mean Value was adjusted for investigative site and baseline severity.

Arms	Assigned Interventions
Experimental: Compound 1 HCl	Drug: Drug: Compound 1 HCl Participants received 30 mg Compound 1 HCl (po, QD) for 1 week followed by 5 weeks at 60 mg in the acute placebo-controlled period. If the participant completes the double-blind portion of the trial, the participant will be offered the option to participate in the open-label

	extension period (given 10, 20, or 40 mg QD for 12 weeks).
Placebo Comparator: Placebo	Drug: Placebo Participants received placebo oral (po), once daily (QD) for 6 weeks (acute phase). If the participant completes the 6-week double-blind portion of the trial, the participant will be offered the option to participate in the open-label extension period (given 10, 20, or 40 milligrams [mg] QD for 12 weeks).

Example 11: Use of Compound 1 HCl for the Treatment of Inflammatory Bowel Disease (IBD)

[00297] The purpose of this study study is to examine in a double blind placebo controlled fashion the effect of Compound 1 HCl on disease activity in patients with IBD.

[00298] Patients: Eligible subjects will be men and women 20 years to 80 years of age.

[00299] Criteria:

Inclusion Criteria:

- Patients with a diagnosis IBD at least 3 months before recruitment will be eligible to the study.
- Patients with active disease who are resistant to either 5 ASA, steroids or immunomodulators
- Disease activity index of either CDAI of more then 200 in Crohn's disease or Mayo score above 3 in UC.
- Age above 20

Exclusion Criteria:

- Patients with a known mental disorder
- Pregnant women
- Patients who are sensitive to any of the ingredients of the study medication.
- Patients who are unable to give informed consent.
- Patients who may need surgery in the near future.

Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment

- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Reduction of 70 points in CDAI [Time Frame: 8 weeks] [Designated as safety issue: No].

Secondary Outcome Measures:

- Change change in quality of life during the study [Time Frame: 8 weeks]

[Designated as safety issue: No]

- Any adverse events during study period [Time Frame: 8 weeks]

[Designated as safety issue: Yes]

Arms	Assigned Interventions
Experimental: Compound 1 HCl	Drug: Compound 1 HCl Compound 1 HCl, twice a day, orally
Placebo Comparator: Placebo	Drug: Placebo Placebo, twice a day, orally

Example 12: Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate the Efficacy and Safety of Compound 1 HCl in the Prophylaxis of Migraine

[00300] The purpose of this study is to evaluate the safety and efficacy of three doses of Compound 1 HCl (10 mg, 20 mg, and 40 mg taken daily) compared with placebo in the prevention of migraine.

[00301] Patients: Eligible subjects will be men and women 18 years to 65 years of age.

[00302] Criteria:

Inclusion Criteria:

- Medical history consistent with migraine with or without aura according to the International Headache Society (IHS) for at least 6 months prior to the study
- Between 3 to 12 migraine periods and no greater than 15 headache days (migraine and non-migraine) per month during the Baseline Phase
- No clinically significant abnormalities on neurological exams, electrocardiogram (ECG) or clinical laboratory test results at baseline

- Female patients must be postmenopausal for at least 1 year, surgically incapable of childbearing, practicing abstinence, or practicing an acceptable method of contraception (requires negative pregnancy test)
- Exclusion Criteria:
- Patients with headaches other than migraine
- Patients with episodic tension or sinus headaches
- Onset of migraine after age of 50 years
- Patients who have failed more than two adequate regimens for migraine prophylaxis
- Patients who overuse pain medications or certain other medications

Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Changes in length of time between the onset and cessation of painful migraine symptoms (migraine period) from the baseline. Safety evaluations conducted throughout the study.

Secondary Outcome Measures:

- Proportion of patients responding to the treatment. Changes from baseline to double-blind phase in number of monthly migraine attacks, monthly migraine days, number of days/month requiring rescue medication, and Health-Related Quality of Life measures.

[00303] This is a randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the effectiveness and safety of three different doses of Compound 1 HCl (10 mg, 20 mg, and 40 mg daily) in migraine prophylaxis. The study consists of five phases: baseline (determination of whether patients meet the eligibility criteria and tapering of any migraine medication patients are already taking); initial titration and double-blind phase (8 weeks) which begins with 5 mg/daily increasing to the assigned (10, 20, and 40 mg/day Compound 1 HCl); followed by a maintenance period at the target dose (18 weeks); tapering transition phase (up to 7 weeks); doses are adjusted to maximize effectiveness and minimize side effects. The primary study hypothesis is that one or more of the three doses of Compound 1 HCl (10, 20, and 40 mg/day) will be superior to placebo in the prophylaxis of migraine based on the change in monthly (28 day) migraine period rate from the prospective baseline period to the double-blind phase and that Compound 1 HCl treatment is well tolerated. During the

titration period (8 weeks), doses are increased to target dose of daily Compound 1 HCl (10, 20, and 40 mg) or placebo, taken twice daily by mouth. Doses are continued for 18 weeks, adjusted over 7 weeks, and continued for up to 6 months during the Open-Label Extension.

Example 13: Study of Compound 1 HCl in the Treatment of Patients With Acute Pain From Bunionectomy

[00304] The purpose of this study is to evaluate the effect of Compound 1 HCl on pain in bunionectomy.

[00305] Patients: Eligible subjects will be men and women over 20-80 years of age.

[00306] Criteria:

Inclusion Criteria:

- Patients who are undergoing primary unilateral first metatarsal bunionectomy that includes a distal Chevron osteotomy only with or without the Akin procedure
- Healthy or medically stable on the basis of clinical laboratory tests performed at screening. If results are outside the normal reference ranges, the patient may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study
- Women must be postmenopausal, surgically sterile, abstinent, or practicing or agree to practice an effective method of birth control if they are sexually active before entry and throughout the study. **Women of childbearing potential must have a negative serum β human chorionic gonadotropin pregnancy test at screening and a negative urine pregnancy test before surgery**
- If a male and sexually active, agrees to use an approved method of birth control to prevent pregnancy in his female partner and not to donate sperm from the day of first study drug intake until 3 months after the day of last study drug intake. To qualify for entry into the double-blind treatment period, the following criteria must be met:
- Qualifying baseline pain intensity (PI) must be rated as greater than or equal to 4 on an 11-point (0 to 10) PI numerical rating scale (NRS), recorded within 30 minutes before randomization
- Qualifying PI must occur no earlier than 10 hours after the first surgical incision
- Qualifying baseline PI must occur within 9 hours after termination of the systemic analgesia during the postoperative surgical period
- Exclusion Criteria:
- History of seizure disorder or epilepsy suggested by the presence of mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year of

screening, and/or severe traumatic brain injury, episode(s) of unconsciousness of more than 24 hours duration, or posttraumatic amnesia of more than 24 hours duration within 15 years of screening

- History of malignancy within the past 2 years before the start of the study
- Evidence of active infections that may spread to other areas of the body or a history of human immunodeficiency virus 1 or 2
- Clinical laboratory values reflecting severe renal insufficiency
- Moderately or severely impaired hepatic function, or patients with abnormal alanine aminotransaminase or aspartate aminotransferase
- Clinical laboratory values outside acceptable limits for surgery in the opinion of the investigator
- A clinically significant disease that in the investigator's opinion may affect efficacy or safety assessments
- Treated with anticonvulsants, monoamine oxidase inhibitors, tricyclic antidepressants, neuroleptics, or serotonin norepinephrine reuptake inhibitor within 2 weeks before randomization
- Systemic steroid therapy, excluding inhalers or topical steroids, within the 4 weeks before screening
- Women who plan to become pregnant during the study, or who are breast feeding

Study Design:

- Allocation: Randomized
- Endpoint Classification: Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Sum of Pain Intensity Differences (SPID) Over 48 Hours [Time Frame: 48 hours] Intensity (PI) is assessed on an 11-point numerical rating scale from 0=no pain to 10=pain as bad as you can imagine. PID is the difference between baseline PI (prior to the first dose) and current PI at assessment. SPID is calculated as the time-weighted Sum of PID scores over 48 hours. Total score ranges from -480 (worst) to 480 (best) for SPID48. A higher value of SPID indicates greater pain relief.

Secondary Outcome Measures:

- Time to First Rescue Medication Use [Time Frame: Up to 48 hours]
[Designated as safety issue: No]
- Reduction in Pain Intensity From Baseline at 12, 24, 48, and 72 Hours
[Time Frame: Baseline (Day 1) and 12, 24, 48, and 72 hours]
[Designated as safety issue: No]

[00307] This is a randomized, double-blind (neither physician nor patient knows the name of the assigned drug), placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of Compound 1 HCl 25 mg and 50 mg in patients who are undergoing bunionectomy (a surgical procedure to remove a bunion). The study will be divided into screening period, surgical period, qualification period, and a double-blind treatment period. The study length, including the screening period, will be up to a maximum duration of 32 days. Eligible patients will be randomly assigned to 1 of 3 treatment groups (Compound 1 HCl 25 mg, Compound 1 HCl 50 mg or placebo) in a 1:1:1 ratio. Efficacy and safety assessments will be performed during the study.

Example 14: Opioids With or Without Compound 1 HCl in Treating Patients With Moderate to Severe Cancer Pain

[00308] The purpose of this study is to see how well opioids work when given together with or without Compound 1 HCl in treating patients with moderate to severe cancer pain.

[00309] Patients: Eligible subjects will be men and women 18-70 years of age.

[00310] Criteria:

- Moderate to severe cancer pain
 - Pain score $\geq 7/10$ (0-10 numeric pain rating scale)
 - Requires strong opioids (step 3) for pain control or are already on stable doses of step 3 opioids
- Opioid induced cognitive dysfunction or cognitive impairment
- Life expectancy ≥ 3 months
- Normal renal function
- Not pregnant or nursing
- Negative pregnancy test
- Must have a telephone
- Able to complete patient questionnaires alone or with assistance
- No delirium
- No hepatic dysfunction
- No nursing home patients
- No intractable nausea or vomiting
- No true allergy or intolerance to opioids
- No gastrointestinal pathology that influences absorption of opioids
- No drug seeking behavior or recent substance abuse history

- No major depression
- No respiratory compromise
- No evidence of severe or uncontrolled systemic disease (e.g., unstable or uncompensated respiratory, cardiac, hepatic, or renal disease)
- No evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the study
- More than 1 month since prior radiotherapy, chemotherapy, or radionuclides
- More than 1 month since prior bisphosphonates
- No prior surgery that influences absorption of opioids
- No concurrent therapeutic procedures or treatments that influence pain
- No concurrent active radiation or antineoplastic therapies
- No concurrent retroviral therapies
- No concurrent drugs that interfere with CYP3A4, CYP1A2, or CYP2D6
- No concurrent drugs that interfere with morphine metabolism
- No concurrent medications that will influence the disposition of morphine or methadone
- No other concurrent antiemetics, antianxiety, or neuroleptic agents

Study Design:

- Allocation: Randomized
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Supportive Care

Primary Outcome Measures:

- Two-point pain improvement from baseline (0-10 numeric **pain** rating scale)

[Designated as safety issue: No]

Secondary Outcome Measures:

- Comparison of active treatment vs placebo [Designated as safety issue: No]
- Effect of Compound 1 HCl on opioid adverse effects [Designated as safety issue: No]
- Relationships between endpoints [Designated as safety issue: No]

Arms	Assigned Interventions
Active Comparator: Arm I Patients receive oral opioid and oral placebo once daily for 4 weeks.	Other: placebo Given orally
Experimental: Arm II	Drug: Compound 1 HCl

Patients receive oral opioid and 50 mg oral Compound 1 HCl once daily for 4 weeks.	Given orally
Experimental: Arm III Patients receive oral opioid and 100 mg oral Compound 1 HCl once daily for 4 weeks.	Drug: Compound 1 HCl Given orally

Example 15: Study of Compound 1 HCl to Treat Osteoarthritis Pain

[00311] The purpose of this study is to evaluate the effect of Compound 1 HCl on osteoarthritis pain of the hip or knee.

[00312] Patients: Eligible subjects will be men and women over 40 years of age.

[00313] Criteria:

Inclusion Criteria:

- Primary diagnosis of Functional Class I-III OA of the hip or knee with documented osteoarthritis flare at baseline
- Chronic user of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen for OA pain
- Discontinued all analgesic therapy at screening
- For women of child-bearing potential: a woman who is not pregnant and not nursing, and who is practicing an acceptable method of birth control

Exclusion Criteria:

- Requires continuous use of opioid or opioid combination products to control OA pain of the knee or hip
- Clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease
- Significant difficulties swallowing capsules or unable to tolerate oral medication
- Previous participation in another clinical study of Compound 1 HCl or received any investigational drug or device or investigational therapy within 30 days before screening

Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Change From Baseline to Week 12 After Trial Entry in Osteoarthritis Pain Measured on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score. [Time Frame: Baseline to Week 12/Early Termination]
[Designated as safety issue: No]. The pain in subjects with osteoarthritis is measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score. The WOMAC pain subscale score is calculated as the average of the visual analogue scale (VAS) scores from 5 pain subscale questions. Subjects mark the VAS, which is a horizontal line 100 mm in length, with a single vertical line to indicate their pain level over the last 24 hours, with 0 mm representing "No Pain" and 100 mm representing "Extreme Pain". The WOMAC pain subscale score difference is calculated as the WOMAC pain subscale score assessed at Week 12 minus the WOMAC pain subscale score assessed at baseline.

Secondary Outcome Measures:

- Change From Baseline to Week 2 After Trial Entry in Osteoarthritis Pain Measured on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score
- Change From Baseline to Week 6 After Trial Entry in Osteoarthritis Pain Measured on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score
- Change From Baseline to the Average of Weeks 2, 6, and 12 After Trial Entry in Osteoarthritis Pain Measured on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Subscale Score

Arms	Assigned Interventions
Experimental: Compound 1 HCl 25 mg bid	Drug: Compound 1 HCl 25 mg bid
Experimental: Compound 1 HCl 25 mg tid	Drug: Compound 1 HCl 25 mg tid
Placebo Comparator: Placebo	Drug: Placebo

Example 16: Phase 3 Study Comparing 2 Doses of Compound 1 HCl vs. Placebo for Treatment of Rheumatoid Arthritis

[00314] The purpose of this study is to evaluate the effect of Compound 1 HCl on improving signs and symptoms and physical function in rheumatoid arthritis patients.

[00315] Patients: Eligible subjects will be men and women over 40 years of age.

[00316] Criteria:

Inclusion Criteria:

- The patient has a diagnosis of RA based upon the American College of Rheumatology (ACR) 1987 Revised Criteria.
- The patient has active disease at both Screening and Baseline, as defined by both: ≥ 6 joints tender or painful on motion; and ≥ 6 joints swollen; and fulfills 1 of the following 2 criteria at Screening: 1. ESR (Westergren method) > 28 mm in the local laboratory. 2. CRP > 7 mg/L in the central laboratory
- Patient had an inadequate response to at least one DMARD (traditional or biologic) due to lack of efficacy or toxicity.
- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis.
- Patient has washed out of all DMARDs other than antimalarials

Exclusion Criteria:

- Blood dyscrasias including confirmed: 1. Hemoglobin < 9 g/dL or Hematocrit $< 30\%$; 2. White blood cell count $< 3.0 \times 10^9/L$; 3. Absolute neutrophil count $< 1.2 \times 10^9/L$; 4. Platelet count $< 100 \times 10^9/L$
- History of any other autoimmune rheumatic disease other than Sjogren's syndrome
- No malignancy or history of malignancy.
- History of infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug.

Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Percentage of Participants Achieving American College of Rheumatology 20% (ACR20) Response at Month 3 [Time Frame: Month 3] [Designated as safety issue: No]. ACR20 response: greater than or equal to ($\geq$) 20 percent (%) improvement in tender joint count; $\geq$ 20% improvement in swollen joint count; and $\geq$ 20% improvement in at least 3 of 5 remaining ACR core measures: participant assessment of pain; participant global assessment of disease activity; physician global assessment of disease activity; self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ]); and C-Reactive Protein (CRP).
- Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Month 3 [Time Frame: Baseline, Month 3] [Designated as safety issue: No]. HAQ-DI: participant-reported assessment of ability to perform tasks in 8 functional categories of daily living activities: dress/groom; arise; eat; walk; reach; grip; hygiene; and common activities over past week. Each item scored on 4-point scale from 0 to 3: 0=no difficulty; 1=some difficulty; 2=much difficulty; 3=unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3, 0=least functional difficulty and 3=extreme functional difficulty.
- Percentage of Participant With Disease Activity Score Using 28-Joint Count and Erythrocyte Sedimentation Rate (4 Variables) (DAS28-4 [ESR]) Less Than 2.6 at Month 3 [Time Frame: Month 3] [Designated as safety issue: No]. DAS28-4 (ESR) calculated from swollen joint count (SJC) and tender/painful joint count (TJC) using 28 joint count, erythrocyte sedimentation rate (ESR) (millimeters per hour [mm/hour]) and patient's global assessment (PtGA) of disease activity (transformed score ranging 0 to 10; higher score indicated greater affectation due to disease activity). Total score range: 0 to 9.4, higher score indicated more disease activity. DAS28-4 (ESR) less than or equal to ($\leq$) 3.2 implied low disease activity, greater than ($>$) 3.2 to 5.1 implied moderate to high disease activity and less than ($<$) 2.6=remission.

Secondary Outcome Measures:

- Percentage of Participants Achieving American College of Rheumatology 20% (ACR20) Response at Week 2, Month 1 and 2 [Time Frame: Week 2, Month 1 and 2] [Designated as safety issue: No].

- Percentage of Participants Achieving American College of Rheumatology 20% (ACR20) Response at Month 4, 5, and 6 [Time Frame: Month 4, 5, and 6]
[Designated as safety issue: No].
- Percentage of Participants Achieving American College of Rheumatology 50% (ACR20) Response at Week 2, Month 1 and 2 [Time Frame: Week 2, Month 1 and 2]
[Designated as safety issue: No].
- Percentage of Participants Achieving American College of Rheumatology 50% (ACR20) Response at Month 4, 5, and 6 [Time Frame: Month 4, 5, and 6]
[Designated as safety issue: No].

Arms	Assigned Interventions
Experimental: Compound 1 HCl 10 mg	Drug: Compound 1 HCl 10 mg Compound 1 HCl BID PO for 6 months
Experimental: Compound 1 HCl 25 mg	Drug: Compound 1 HCl 25 mg Compound 1 HCl BID PO for 6 months
Placebo Comparator: Placebo Sequence 1	Drug: Placebo Placebo patients advance to 10 mg Compound 1 HCl BID at Month 3 visit
Placebo Comparator: Placebo Sequence 2	Drug: Placebo Placebo patients advance to 25 mg Compound 1 HCl BID at Month 3 visit

Example 17: Effect of Compound 1 HCl in the Treatment of Patients With Chemotherapy Induced Peripheral Neuropathy

[00317] The purpose of this study is to evaluate the effect of to test the effect of Compound 1 HCl on peripheral neuropathy scores after 6 weeks treatment and is based on the separate assessment of pain and dysesthesia scores.

[00318] Patients: Eligible subjects will be men and women over 18-80 years of age.

[00319] Criteria:

Inclusion Criteria:

- Have signed an Informed Consent to participate to the trial before any study related procedure has taken place.
- Be >18 years and if a female with adequate contraception if of child bearing potential.

- Have paclitaxel (or other taxane) induced peripheral neuropathy assessed by the presence of a NCI-CTC version 2 neuropathy sensory grade ≥ 2 .
- Peripheral neuropathy as clinically diagnosed during the neurological examination including sensitivity, motor function and deep tendon reflex assessments
- With Neuropathic pain as assessed by the presence of measurable pain perception (previous 24h) on the Likert numerical rating scale ≥ 4 points at the screening visit and confirmed on DN4 with a score ≥ 4 and/or dysesthesia as assessed by the presence of measurable dysesthesia (previous 24h) on the Likert numerical rating scale ≥ 4 points at the screening visit
- Persistent neuropathy for at least 3, but no more than 12 months after the end of chemotherapy.
- Be either pain treatment naive or have important side effects or inadequate relief from their current pain medication (stable over last month).

Exclusion Criteria:

- Have a documented neuropathy or risk factors of neuropathy which might interfere with the assessment of the severity of pain (eg, including, but not limited to, type 2 diabetes, peripheral vascular disease, B12 Vitamin deficiency, thyroid dysfunction, post surgical neuropathic pain, post-traumatic neuropathy, or neuropathy in relation with disease progression).
- Have other neurological diseases that may produce weakness, sensory loss, or autonomic symptoms, or laboratory test abnormality.
- Refractory to treatment defined as not improved, according to the Investigator, by 3 or more treatments prescribed for the current PN symptoms.
- HIV positive serology.
- History of, or current cardiac dysrhythmias and / or a history of cardiovascular disease, including myocardial infarction, except patients with only well controlled hypertension.
- Have had prior (within the past 6 months) or have concurrent neurotoxic drugs (e.g., but not limited to, cisplatin, vincristine, vinblastine, cytarabine, thalidomide, bortezomib, or procarbazine, capecitabine, navelbine).
- Have a current medication of lipid lowering agents other than statins.
- Have a recent history (within the previous 6 months) or current evidence of alcohol or drug abuse.
- Have concurrent unstable disease involving any system (eg, advanced carcinoma other than carcinoma justifying the recent treatment with taxanes, myocardial infarction, clinical or ECG signs of myocardial ischemia, cardiac insufficiency, anginal symptoms, current

symptoms of CAD, renal impairment, or any other condition that in the opinion of the Investigator would make the patient unsuitable for study participation)

- Be pregnant female or lactating.
- Have renal impairment defined as blood creatinine $> 1.5 \times$ upper limit of normal (ULN)
- Hemostasis disorders or current treatment with oral anticoagulants.
- Have hepatic impairment hepatic function as follows: liver enzymes (ALT and AST) $> 2 \times$ ULN or $> 3.5 \times$ ULN in case of liver metastasis
- Participated in any other investigational drug or therapy study with a non approved medication, within the previous 3 months.
- Any other condition which, in the opinion of the investigator would impede competence or compliance or possibly hinder completion of the study

Study Design:

- Allocation: Randomized
- Endpoint Classification: Safety/Efficacy Study
- Intervention Model: Parallel Assignment
- Masking: Double Blind (Subject, Investigator)
- Primary Purpose: Treatment

Primary Outcome Measures:

- Percentage of responders defined as patients with a minimum decrease of 50 % of their maximum neuropathic pain dimension (either pain or dysesthesia) present at baseline.
[Time Frame: The mean pain score during the last 7 days of the treatment period will be compared to the mean score of the last 7 days of the screening score period.]
[Designated as safety issue: No].

Secondary Outcome Measures:

- Assessment with respect to placebo of the effect of Compound 1 HCl on Neuropathic Pain Inventory Score (total and by dimension) [Time Frame: Screening visit; V0; V1; V2; V3; V4 ; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on Short- Form BPI [Time Frame: Screening visit; V0; V1; V2; V3; V4 ; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on Quality of life questionnaire (CIPN 20) [Time Frame: V0; V3; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on Dysgeusia questionnaire [Time Frame: V0; V3; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on Quantitative Sensory Testing [Time Frame: V0; V3; V5] [Designated as safety issue: No]

- Assessment with respect to placebo of the effect of Compound 1 HCl on ENMG [Time Frame: V0; V3; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on the use of rescue medication [Time Frame: Screening visit; V0; V1; V2; V3; V4 ; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on safety profile [Time Frame: Screening visit; V0; V1; V2; V3; V4 ; V5] [Designated as safety issue: Yes]
- Assessment with respect to placebo of the effect of Compound 1 HCl on Global Impression of change as assessed by Investigator [Time Frame: V1; V2; V3; V4; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on Global Impression of change as assessed by patient [Time Frame: V1; V2; V3; V4; V5] [Designated as safety issue: No]
- Assessment with respect to placebo of the effect of Compound 1 HCl on Hospital Anxiety and Depression scale [Time Frame: V0;V3;V5] [Designated as safety issue: No]

Arms	Assigned Interventions
Experimental: Compound 1 HCl (40 mg) once a day	Drug: Compound 1 HCl Compound 1 HCl (40 mg) once a day
Placebo Comparator: Control Placebo once a day	Drug: Placebo Control Placebo once a day

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 500 mg.
2. A method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg.
3. A method of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the effective dose is from about 1 mg to about 100 mg.
4. A method of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein a fragment of Compound 1 is covalently attached to at least 30% of MGLL in PBMCs from the patient after administration of the effective dose.
5. A method of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-

- (trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the plasma AUC_{0-inf} of Compound 1 is at least $0.05 \mu M \cdot hr$ after administration of the effective dose.
6. A method of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least $0.05 \mu M \cdot hr$ after administration of the effective dose.
 7. The method of claim 4, wherein a fragment of Compound 1 is covalently attached to at least 40% of MGLL in PBMCs from the patient after administration of the effective dose.
 8. The method of claim 4, wherein a fragment of Compound 1 is covalently attached to at least 50% of MGLL in PBMCs from the patient after administration of the effective dose.
 9. The method of claim 4, wherein a fragment of Compound 1 is covalently attached to at least 60% of MGLL in PBMCs from the patient after administration of the effective dose.
 10. The method of claim 4, wherein a fragment of Compound 1 is covalently attached to at least 70% of MGLL in PBMCs from the patient after administration of the effective dose.
 11. The method of claim 4, wherein a fragment of Compound 1 is covalently attached to at least 80% of MGLL in PBMCs from the patient after administration of the effective dose.
 12. The method of claim 4, wherein a fragment of Compound 1 is covalently attached to at least 90% of MGLL in PBMCs from the patient after administration of the effective dose.
 13. The method of any one of claims 4 and 7-12, wherein measurement of fragments of Compound 1 covalently attached to MGLL in PBMCs from the patient is performed using an *in vitro* assay.
 14. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least $0.1 \mu M \cdot hr$ after administration of the effective dose.
 15. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least $0.2 \mu M \cdot hr$ after administration of the effective dose.

16. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.3 $\mu M \cdot hr$ after administration of the effective dose.
17. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.4 $\mu M \cdot hr$ after administration of the effective dose.
18. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.5 $\mu M \cdot hr$ after administration of the effective dose.
19. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.6 $\mu M \cdot hr$ after administration of the effective dose.
20. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.7 $\mu M \cdot hr$ after administration of the effective dose.
21. The method of claim 5, wherein the plasma AUC_{0-inf} of Compound 1 is at least 0.8 $\mu M \cdot hr$ after administration of the effective dose.
22. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.1 $\mu M \cdot hr$ after administration of the effective dose.
23. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.2 $\mu M \cdot hr$ after administration of the effective dose.
24. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.3 $\mu M \cdot hr$ after administration of the effective dose.
25. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.4 $\mu M \cdot hr$ after administration of the effective dose.
26. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.5 $\mu M \cdot hr$ after administration of the effective dose.
27. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.6 $\mu M \cdot hr$ after administration of the effective dose.
28. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.7 $\mu M \cdot hr$ after administration of the effective dose.
29. The method of claim 6, wherein the steady state plasma AUC_{0-inf} of Compound 1 is at least 0.8 $\mu M \cdot hr$ after administration of the effective dose.
30. The method of any one of claims 4-29, wherein the effective dose is from about 1 mg to about 500 mg.
31. The method of any one of claims 1 and 4-29, wherein the effective dose is from about 2 mg to about 400 mg.
32. The method of any one of claims 1 and 4-29, wherein the effective dose is from about 10 mg to about 160 mg.

33. The method of any one of claims 1-29, wherein the effective dose is from about 2 mg to about 100 mg.
34. The method of any one of claims 1-29, wherein the effective dose is from about 2 mg to about 50 mg.
35. The method of any one of claims 1-29, wherein the effective dose is from about 2 mg to about 20 mg.
36. The method of any one of claims 1-35, wherein Compound 1 is administered orally.
37. The method of claim 36, wherein the effective dose is taken with food.
38. The method of claim 36, wherein the effective dose is taken without food.
39. The method of any one of claims 1-38, wherein the effective dose is administered to the patient once per day.
40. The method of any one of claims 1-38, wherein the effective dose is administered to the patient twice per day.
41. A method of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.05 \mu M \cdot hr$.
42. The method of claim 41, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.1 \mu M \cdot hr$.
43. The method of claim 41, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.2 \mu M \cdot hr$.
44. A method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.05 \mu M \cdot hr$.
45. The method of claim 44, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.1 \mu M \cdot hr$.
46. The method of claim 44, wherein administration of the composition provides a plasma AUC_{0-inf} of at least $0.2 \mu M \cdot hr$.

47. A method of treating acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides a plasma $AUC_{0-\infty}$ of at least $0.05 \mu M \cdot hr$.
48. A method of treating inflammation or neuropathic pain in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.
49. A method of treating Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome in a patient in need thereof, comprising administering to the patient in need thereof a composition comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, wherein administration of the composition provides at least 30% of MGLL in PBMCs from the patient to be covalently attached to a fragment of Compound 1.
50. The method of any one of claims 40-49, wherein Compound 1 is administered orally.
51. A method of binding MGLL with 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1) in PBMCs in a subject after administration of an effective dose of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject, wherein a fragment of Compound 1 is covalently attached to at least 30% MGLL in PBMCs.
52. The method of claim 51, wherein a fragment of Compound 1 is covalently attached to at least 40% of MGLL in PBMCs from the subject after administration of the effective dose.

53. The method of claim 51, wherein a fragment of Compound 1 is covalently attached to at least 50% of MGLL in PBMCs from the subject after administration of the effective dose.
54. The method of claim 51, wherein a fragment of Compound 1 is covalently attached to at least 60% of MGLL in PBMCs from the subject after administration of the effective dose.
55. The method of claim 51, wherein a fragment of Compound 1 is covalently attached to at least 70% of MGLL in PBMCs from the subject after administration of the effective dose.
56. The method of claim 51, wherein a fragment of Compound 1 is covalently attached to at least 80% of MGLL in PBMCs from the subject after administration of the effective dose.
57. The method of claim 51, wherein a fragment of Compound 1 is covalently attached to at least 90% of MGLL in PBMCs from the subject after administration of the effective dose.
58. The method of any one of claims 51-57, wherein the effective dose is from about 1 mg to about 500 mg.
59. The method of any one of claims 51-57, wherein the effective dose is from about 2 mg to about 400 mg.
60. The method of any one of claims 51-57, wherein the effective dose is from about 10 mg to about 160 mg.
61. The method of any one of claims 51-57, wherein the effective dose is from about 2 mg to about 100 mg.
62. The method of any one of claims 51-57, wherein the effective dose is from about 2 mg to about 50 mg.
63. The method of any one of claims 51-57, wherein the effective dose is from about 2 mg to about 20 mg.
64. The method of any one of claims 51-63, wherein Compound 1 is administered orally.
65. A pharmaceutical composition for the treatment of inflammation or neuropathic pain, wherein the pharmaceutical composition comprises an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 500 mg.

66. The pharmaceutical composition of claim 65, wherein the effective dose is from about 2 mg to about 400 mg.
67. The pharmaceutical composition of claim 65, wherein the effective dose is from about 10 mg to about 160 mg.
68. The pharmaceutical composition of claim 65, wherein the effective dose is from about 2 mg to about 100 mg.
69. The pharmaceutical composition of claim 65, wherein the effective dose is from about 2 mg to about 50 mg.
70. The pharmaceutical composition of claim 65, wherein the effective dose is from about 2 mg to about 20 mg.
71. A pharmaceutical composition for the treatment of Epilepsy/Seizure Disorder, Multiple Sclerosis, Neuromyelitis Optica (NMO), Tourette Syndrome, Alzheimer Disease, or abdominal pain associated with Irritable Bowel Syndrome, wherein the pharmaceutical composition comprises an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 100 mg.
72. A pharmaceutical composition for the treatment of acute pain, inflammatory pain, cancer pain, pain caused by peripheral neuropathy, central pain, fibromyalgia, migraine, vasoocclusive painful crises in sickle cell disease, spasticity or pain associated with multiple sclerosis, functional chest pain, rheumatoid arthritis, osteoarthritis, or functional dyspepsia, wherein the pharmaceutical composition comprises an effective dose of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate (Compound 1), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, wherein the effective dose is from about 1 mg to about 100 mg.
73. The pharmaceutical composition of claim 71 or claim 72, wherein the effective dose is from about 2 mg to about 100 mg.
74. The pharmaceutical composition of claim 71 or claim 72, wherein the effective dose is from about 2 mg to about 50 mg.
75. The pharmaceutical composition of claim 71 or claim 72, wherein the effective dose is from about 2 mg to about 20 mg.

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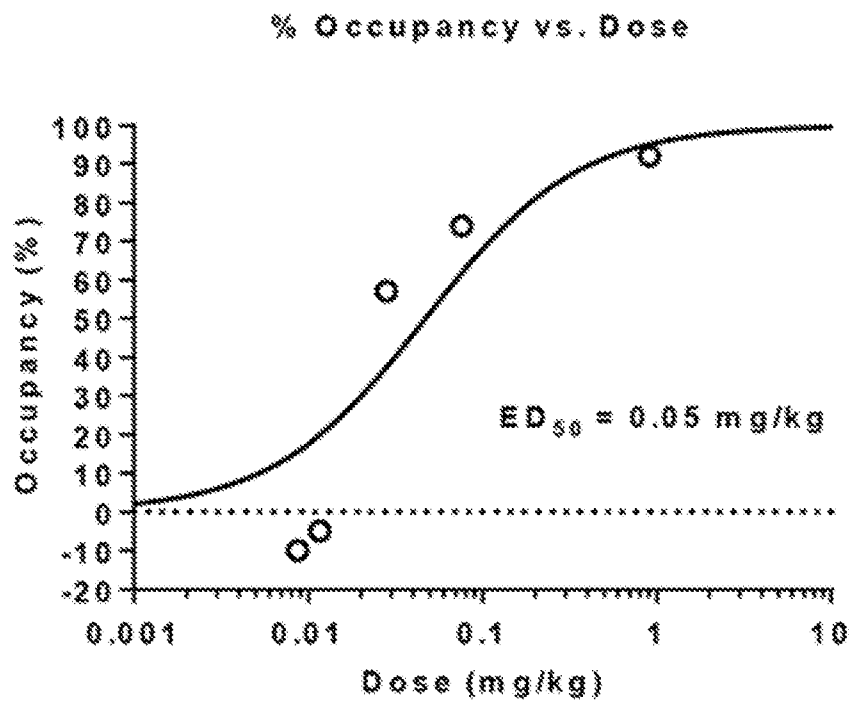


Fig. 1

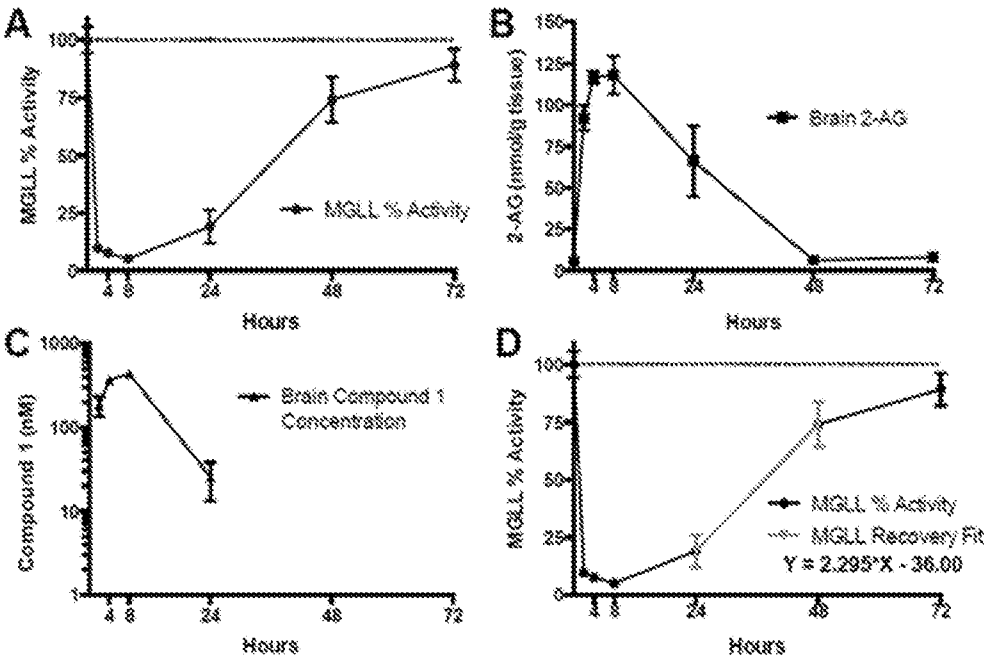


Fig. 2

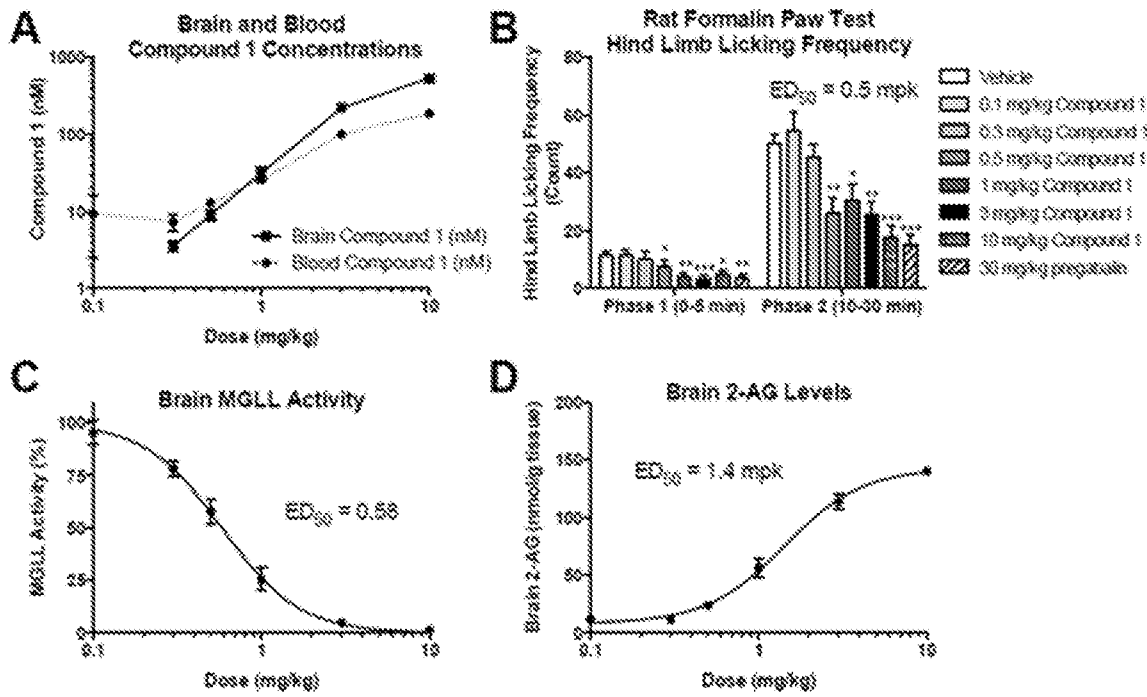


Fig. 3

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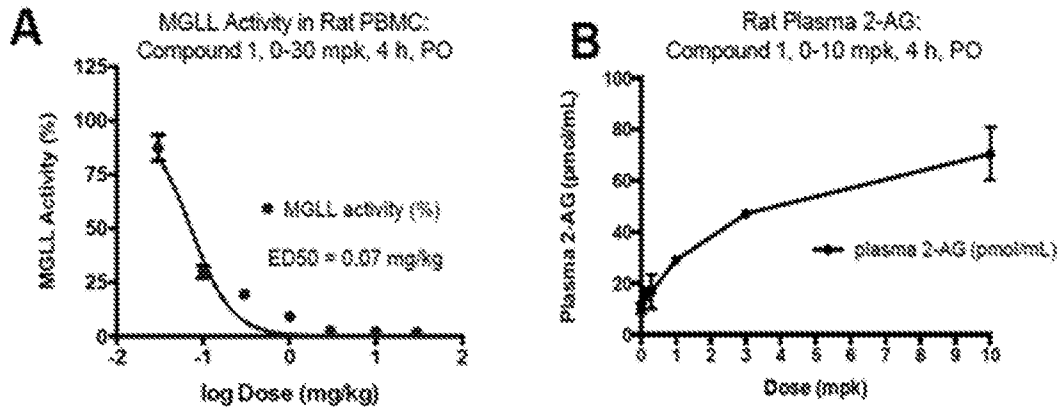


Fig. 4

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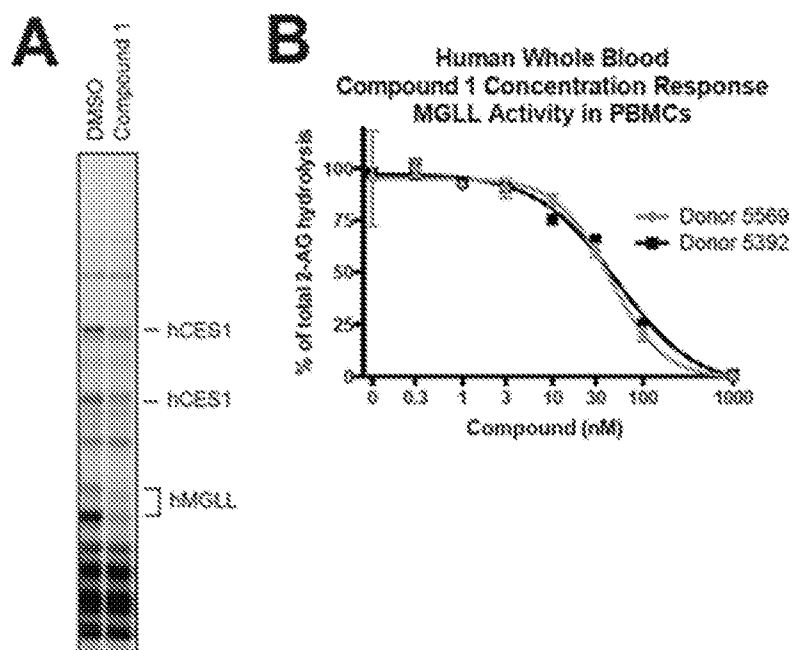


Fig. 5

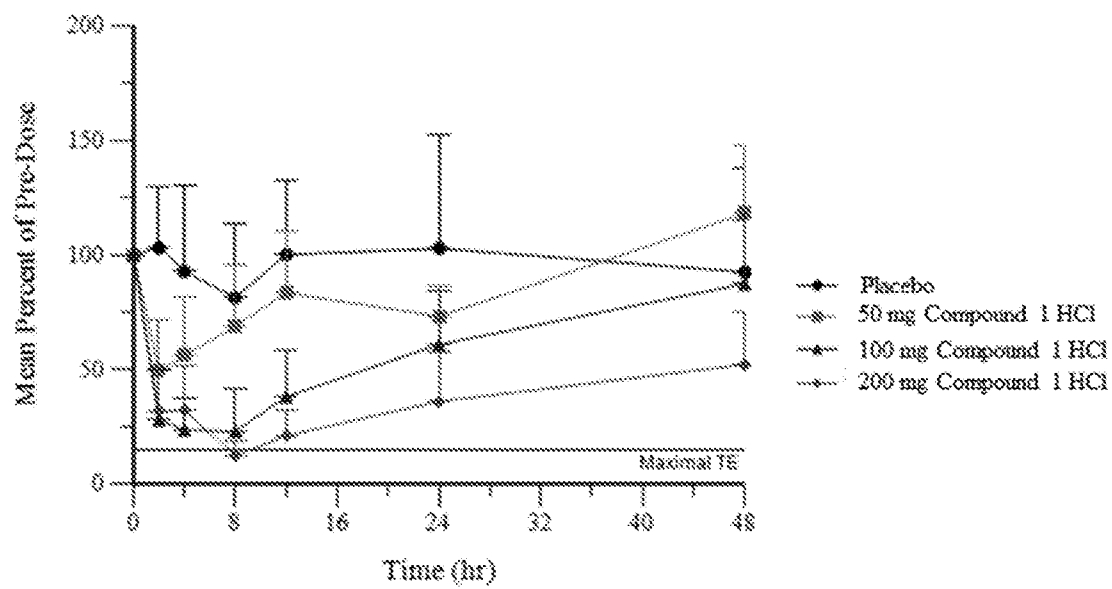


Fig. 6

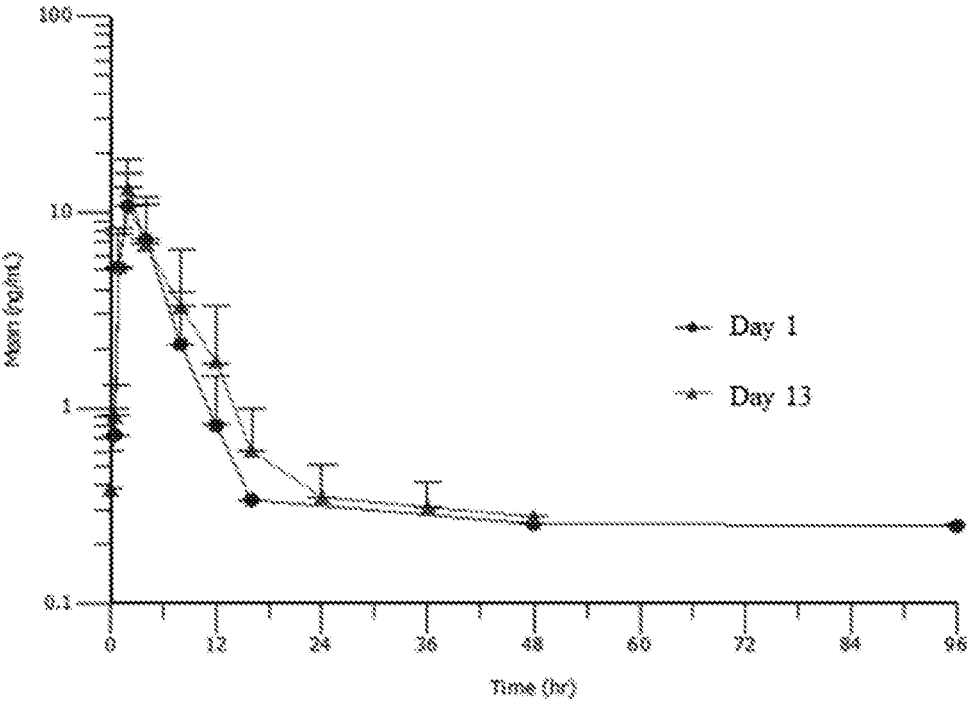


Fig. 7

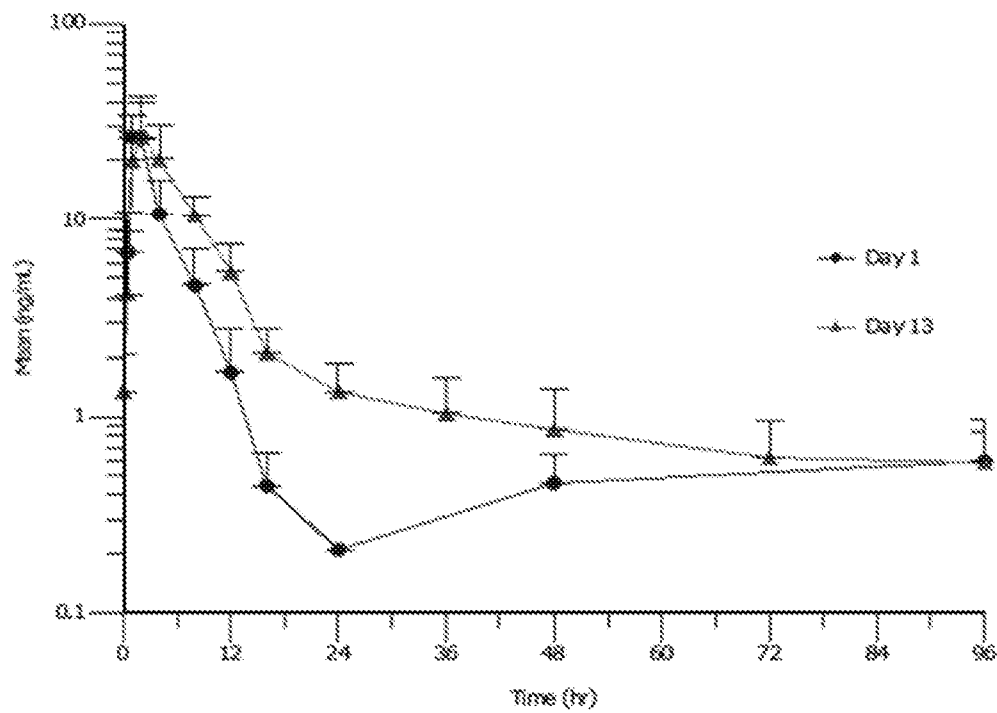


Fig. 8

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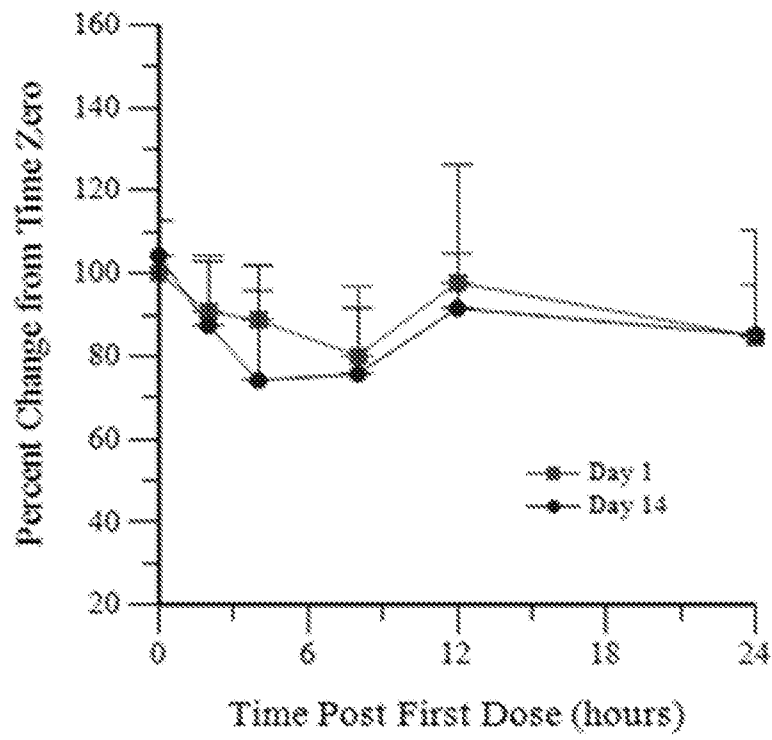


Fig. 9

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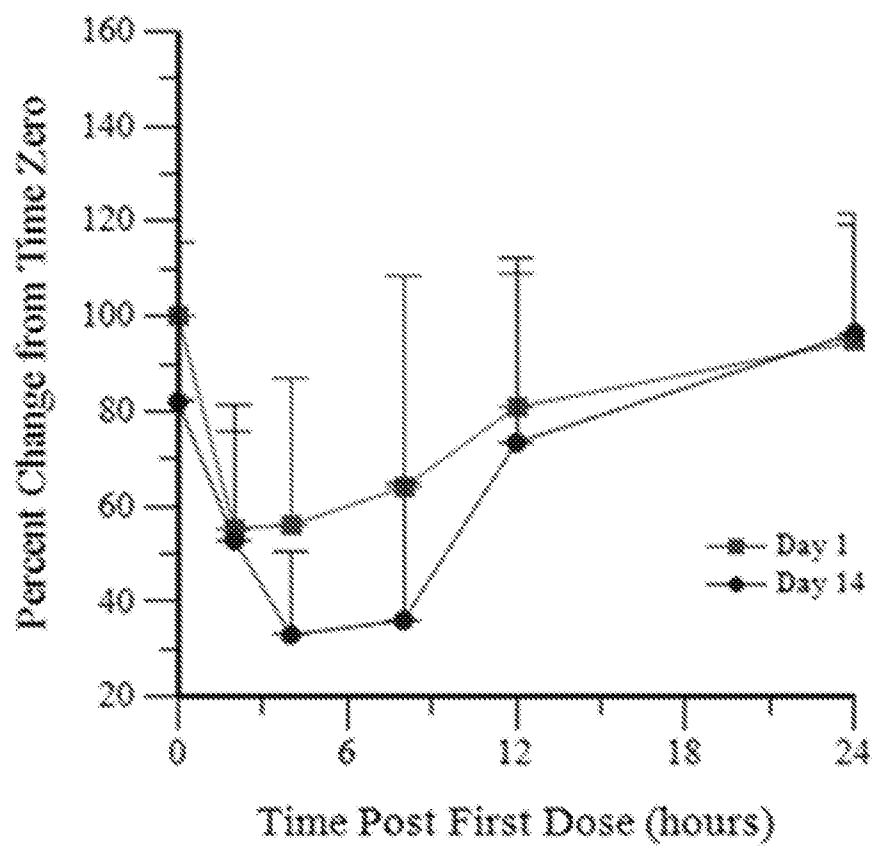


Fig. 10

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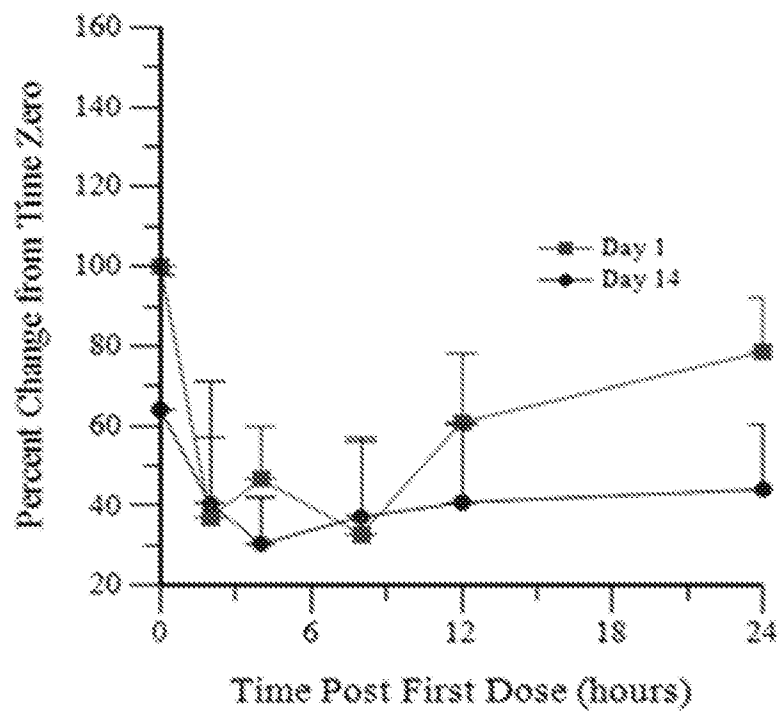


Fig. 11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031668

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 403/10, C07D 213/55, C07D 295/73, C07D 295/192, C07D 295/205, C07D 403/00 (2016.01)

CPC - C07D 403/10, C07D 213/55, C07D 295/73, C07D 295/192, C07D 295/205, C07D 403/00 (2016.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC - C07D 213/55, C07D 295/73, C07D 295/192, C07D 295/205, C07D 403/00, C07D 403/10

CPC - C07D 213/55, C07D 295/73, C07D 295/192, C07D 295/205, C07D 403/00, C07D 403/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC- 514/235.8, 514/357, 514/466; 544/121, 544/389; 549/441; IPC-C07D 213/55, C07D 295/73, C07D 295/192, C07D 295/205, C07D 403/00, C07D 403/10; CPC- C07D 213/55, C07D 295/73, C07D 295/192, C07D 295/205, C07D 403/00, C07D 403/10 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Patents, Google, PubChem, SureChem, STN

Search terms used: inflammation, neuropathic pain, MGLL, Monoacylglycerol lipase, PBMC, peripheral blood mononuclear cell, 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/0018335 A1 (ABIDE THERAPEUTICS INC) 15 January 2015 (15.01.2015) entire document	1-29, 41-49, 51-63, 65-75
A	WO 2013/159095 A1 (ANDERSON GAWECO) 24 October 2013 (24.10.2013) entire document	1-29, 41-49, 51-63, 65-75
A	US 2008/0214524 A1 (LEE et al) 04 September 2008 (04.09.2008) entire document	1-29, 41-49, 51-63, 65-75
A	WO 2010/063802 A1 (NOVARTIS AG et al) 10 June 2010 (10.06.2010) entire document	1-29, 41-49, 51-63, 65-75

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search

12 July 2016

Date of mailing of the international search report

11 AUG 2016

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031668

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

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

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 30-40, 50, 64
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

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



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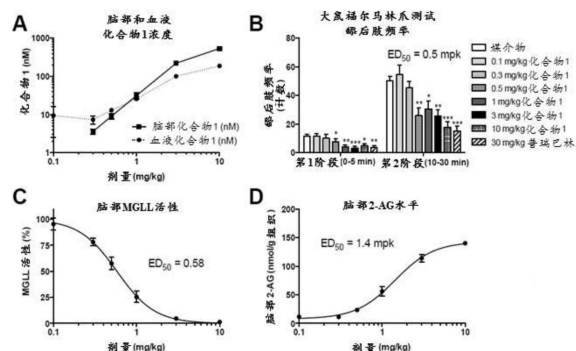
权利要求书5页 说明书74页 附图7页

(54)发明名称

治疗炎症或神经性疼痛的方法

(57)摘要

本文提供了使用有效剂量的单酰基甘油酯
脂肪酶抑制剂或其组合物治疗炎症或神经性疼痛
的方法。



1. 一种治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中所述有效剂量为约1mg至约500mg。

2. 一种治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。

3. 一种治疗有需要的患者的急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。

4. 一种治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少30%的MGLL共价附接。

5. 一种治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.05μM·hr。

6. 一种治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.05μM·hr。

7. 根据权利要求4所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少40%的MGLL共价附接。

8. 根据权利要求4所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少50%的MGLL共价附接。

9. 根据权利要求4所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少60%的MGLL共价附接。

10. 根据权利要求4所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少70%的MGLL共价附接。

11. 根据权利要求4所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少80%的MGLL共价附接。

12. 根据权利要求4所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少90%的MGLL共价附接。

13. 根据权利要求4和7-12中任一项所述的方法,其中采用体外测定对与来自所述患者

的PBMC中的MGLL共价附接的化合物1片段进行测量。

14. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.1 $\mu\text{M} \cdot \text{hr}$ 。

15. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.2 $\mu\text{M} \cdot \text{hr}$ 。

16. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.3 $\mu\text{M} \cdot \text{hr}$ 。

17. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.4 $\mu\text{M} \cdot \text{hr}$ 。

18. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.5 $\mu\text{M} \cdot \text{hr}$ 。

19. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.6 $\mu\text{M} \cdot \text{hr}$ 。

20. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.7 $\mu\text{M} \cdot \text{hr}$ 。

21. 根据权利要求5所述的方法,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.8 $\mu\text{M} \cdot \text{hr}$ 。

22. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.1 $\mu\text{M} \cdot \text{hr}$ 。

23. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.2 $\mu\text{M} \cdot \text{hr}$ 。

24. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.3 $\mu\text{M} \cdot \text{hr}$ 。

25. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.4 $\mu\text{M} \cdot \text{hr}$ 。

26. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.5 $\mu\text{M} \cdot \text{hr}$ 。

27. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.6 $\mu\text{M} \cdot \text{hr}$ 。

28. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.7 $\mu\text{M} \cdot \text{hr}$ 。

29. 根据权利要求6所述的方法,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.8 $\mu\text{M} \cdot \text{hr}$ 。

30. 根据权利要求4-29中任一项所述的方法,其中所述有效剂量为约1mg至约500mg。

31. 根据权利要求1和4-29中任一项所述的方法,其中所述有效剂量为约2mg至约400mg。

32. 根据权利要求1和4-29中任一项所述的方法,其中所述有效剂量为约10mg至约160mg。

33. 根据权利要求1-29中任一项所述的方法,其中所述有效剂量为约2mg至约100mg。

34. 根据权利要求1-29中任一项所述的方法,其中所述有效剂量为约2mg至约50mg。
35. 根据权利要求1-29中任一项所述的方法,其中所述有效剂量为约2mg至约20mg。
36. 根据权利要求1-35中任一项所述的方法,其中口服施用化合物1。
37. 根据权利要求36所述的方法,其中所述有效剂量与食物一起服用。
38. 根据权利要求36所述的方法,其中所述有效剂量在没有食物的情况下服用。
39. 根据权利要求1-38中任一项所述的方法,其中每日一次向所述患者施用所述有效剂量。
40. 根据权利要求1-38中任一项所述的方法,其中每日两次向所述患者施用所述有效剂量。
41. 一种治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。
42. 根据权利要求41所述的方法,其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。
43. 根据权利要求41所述的方法,其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。
44. 一种治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用包含4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。
45. 根据权利要求44所述的方法,其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。
46. 根据权利要求44所述的方法,其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。
47. 一种治疗有需要的患者的急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法,该方法包括向所述有需要的患者施用包含4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。
48. 一种治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐的组合物,其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价衔接。
49. 一种治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用包含4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟

丙烷-2-基酯(化合物1)或其药学上可接受的盐的组合物,其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价附接。

50. 根据权利要求40-49中任一项所述的方法,其中口服施用化合物1。

51. 一种在向受试者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐后,使MGLL与化合物1在所述受试者的PBMC中结合的方法,其中化合物1的片段与PBMC中的至少30%的MGLL共价附接。

52. 根据权利要求51所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少40%的MGLL共价附接。

53. 根据权利要求51所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少50%的MGLL共价附接。

54. 根据权利要求51所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少60%的MGLL共价附接。

55. 根据权利要求51所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少70%的MGLL共价附接。

56. 根据权利要求51所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少80%的MGLL共价附接。

57. 根据权利要求51所述的方法,其中在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少90%的MGLL共价附接。

58. 根据权利要求51-57中任一项所述的方法,其中所述有效剂量为约1mg至约500mg。

59. 根据权利要求51-57中任一项所述的方法,其中所述有效剂量为约2mg至约400mg。

60. 根据权利要求51-57中任一项所述的方法,其中所述有效剂量为约10mg至约160mg。

61. 根据权利要求51-57中任一项所述的方法,其中所述有效剂量为约2mg至约100mg。

62. 根据权利要求51-57中任一项所述的方法,其中所述有效剂量为约2mg至约50mg。

63. 根据权利要求51-57中任一项所述的方法,其中所述有效剂量为约2mg至约20mg。

64. 根据权利要求51-63中任一项所述的方法,其中口服施用化合物1。

65. 一种用于治疗炎症或神经性疼痛的药物组合物,其中所述药物组合物包含有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。

66. 根据权利要求65所述的药物组合物,其中所述有效剂量为约2mg至约400mg。

67. 根据权利要求65所述的药物组合物,其中所述有效剂量为约10mg至约160mg。

68. 根据权利要求65所述的药物组合物,其中所述有效剂量为约2mg至约100mg。

69. 根据权利要求65所述的药物组合物,其中所述有效剂量为约2mg至约50mg。

70. 根据权利要求65所述的药物组合物,其中所述有效剂量为约2mg至约20mg。

71. 一种用于治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的药物组合物,其中所述药物组合物包含有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约

1mg至约100mg。

72. 一种用于治疗急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的药物组合物,其中所述药物组合物包含有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约100mg。

73. 根据权利要求71或权利要求72所述的药物组合物,其中所述有效剂量为约2mg至约100mg。

74. 根据权利要求71或权利要求72所述的药物组合物,其中所述有效剂量为约2mg至约50mg。

75. 根据权利要求71或权利要求72所述的药物组合物,其中所述有效剂量为约2mg至约20mg。

治疗炎症或神经性疼痛的方法

交叉引用

[0001] 本申请要求于2015年5月11日提交的美国临时申请号62/159,770和于2016年2月19日提交的美国临时申请号62/297,670的权益,这两个申请均通过引用以其全文并入本文。

背景

[0002] 单酰基甘油脂肪酶 (MGLL或MAGL) 是神经系统中负责水解内源性大麻素类如2-AG (2-花生四烯酰甘油) ——一种基于花生四烯酸酯的脂质——的酶。

发明内容

[0003] 本文公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中所述有效剂量为约1mg至约500mg。

[0004] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少2倍。

[0005] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少30%的MGLL共价衔接。

[0006] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.05μM·hr。本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.1μM·hr。本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.2μM·hr。

[0007] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.05μM·hr。本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.1μM·hr。本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.2μM·hr。

[0008] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向

所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后:(a)所述患者的血浆2-AG的浓度增加至少2倍;并且(b)化合物1的片段与来自所述患者的PBMC中的至少30%的MGLL共价附接。

[0009] 本文还公开了用作药物的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐。本文进一步公开了用于在治疗人或动物体的炎症、疼痛或神经性疼痛的方法中使用的化合物1或其药学上可接受的盐;其中有效剂量为约1mg至约500mg;或者其中在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少2倍;或者其中在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少30%的MGLL共价附接;或者其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.05μM·hr;或者其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.1μM·hr;或者其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.2μM·hr;或者其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.05μM·hr;或者其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.1μM·hr;或者其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.2μM·hr;或者其中在施用所述有效剂量后:(a)所述患者的血浆2-AG的浓度增加至少2倍;并且(b)化合物1的片段与来自所述患者的PBMC中的至少30%的MGLL共价附接。

[0010] 本文进一步公开了治疗有需要的患者的癫痫(Epilepsy)/癫痫发作(Seizure Disorder)、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。

[0011] 本文进一步公开了治疗有需要的患者的急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。

[0012] 本文还公开了用于在治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病、与肠易激综合征相关的腹痛、急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法中使用的化合物1或其药学上可接受的盐,其中有效剂量为约1mg至约100mg。

[0013] 在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少3倍。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少4倍。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少5倍。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少6倍。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少7倍。在本文所述的方法和医疗用途的

一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少8倍。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少9倍。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少10倍。在本文所述的方法和医疗用途的一些实施方案中,在体外测定中测量所述患者的血浆2-AG的浓度。

[0014] 在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少40%的MGLL共价附接。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少50%的MGLL共价附接。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少60%的MGLL共价附接。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少70%的MGLL共价附接。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少80%的MGLL共价附接。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少90%的MGLL共价附接。在本文所述的方法和医疗用途的一些实施方案中,采用体外测定对与来自所述患者的PBMC中的MGLL共价附接的化合物1片段进行测量。

[0015] 在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.3 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.4 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.5 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.6 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.7 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.8 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.9 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少1.0 $\mu\text{M} \cdot \text{hr}$ 。

[0016] 在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.3 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.4 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.5 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.6 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.7 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.8 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.9 $\mu\text{M} \cdot \text{hr}$ 。在本文所述的方法和医疗用途的一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少1.0 $\mu\text{M} \cdot \text{hr}$ 。

[0017] 在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量为约1mg至约500mg。在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量为约2mg至约400mg。在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量为约10mg至约160mg。在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量为约2mg至约100mg。在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量为约2mg至约50mg。在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量为约2mg至约20mg。

[0018] 在本文所述的方法和医疗用途的一些实施方案中,口服施用化合物1。在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量与食物一起服用。在本文所述的方法和医疗用途的一些实施方案中,所述有效剂量在没有食物的情况下服用。在本文所述的方法和医疗用途的一些实施方案中,每日一次向所述患者施用所述有效剂量。在本文所述的方法和医疗用途的一些实施方案中,每日两次向所述患者施用所述有效剂量。在本文所述的方法和医疗用途的一些实施方案中,每日三次向所述患者施用所述有效剂量。

[0019] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。

[0020] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用将所述患者的血浆2-AG的浓度增加至少2倍。

[0021] 本文进一步公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价衔接。

[0022] 本文还公开了用于在治疗人或动物体的炎症或神经性疼痛的方法中使用的组合物,该组合物包含化合物1或其药学上可接受的盐;其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$;或者其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$;或者其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$;或者其中所述组合物的施用将所述患者的血浆2-AG的浓度增加至少2倍;或者其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价衔接。

[0023] 本文进一步公开了治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文进一步公开了治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文进一步公

开了治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎 (NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。

[0024] 本文进一步公开了治疗有需要的患者的急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文进一步公开了治疗有需要的患者的急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文进一步公开了治疗有需要的患者的急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。

[0025] 本文还公开了用于在治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎 (NMO)、图雷特综合征、阿尔茨海默病、与肠易激综合征相关的腹痛、急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法中使用的组合物,该组合物包含化合物1或其药学上可接受的盐;其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文还公开了用于在治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎 (NMO)、图雷特综合征、阿尔茨海默病、与肠易激综合征相关的腹痛、急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法中使用的组合物,该组合物包含化合物1或其药学上可接受的盐;其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文还公开了用于在治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎 (NMO)、图雷特综合征、阿尔茨海默病、与肠易激综合征相关的腹痛、急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法中使用的组合物,该组合物包含化合物1或其药学上可接受的盐;其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。

[0026] 本文进一步公开了治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎 (NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价衔接。

[0027] 本文进一步公开了治疗有需要的患者的急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价衔接。

[0028] 本文还公开了用于在治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病、与肠易激综合征相关的腹痛、急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法中使用的组合物,该组合物包含化合物1或其药学上可接受的盐;其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价衔接。

[0029] 本文进一步公开了使用有效剂量的化合物1或其药学上可接受的盐增加受试者的血浆2-AG的浓度的方法和医疗用途,其中受试者的血浆2-AG的浓度增加至少2倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少3倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少4倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少5倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少6倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少7倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少8倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少9倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少10倍。

[0030] 本文进一步公开了在向受试者施用有效剂量的化合物1或其药学上可接受的盐后,使MGLL与化合物1在所述受试者的PBMC中结合的方法,其中化合物1的片段与PBMC中的至少30%的MGLL共价衔接。本文进一步公开了用于在本文公开的任一种治疗方法中使用的化合物1或其药学上可接受的盐,其中在施用有效剂量的化合物1后,化合物1的片段与受试者的PBMC中的至少30%的MGLL共价衔接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少40%的MGLL共价衔接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少50%的MGLL共价衔接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少60%的MGLL共价衔接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少70%的MGLL共价衔接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少80%的MGLL共价衔接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述受试者的PBMC中的至少90%的MGLL共价衔接。在一些实施方案中,所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。在一些实施方案中,口服施用化合物1。

[0031] 本文进一步公开了包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂的药物组合物,其中所述有效剂量为约1mg至约500mg。本文进一步公开了用

于治疗炎症或神经性疼痛的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。本文进一步公开了用于在治疗人或动物体的炎症或神经性疼痛的方法中使用的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0032] 本文进一步公开了用于治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。本文进一步公开了用于在治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法中使用的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0033] 本文进一步公开了用于治疗急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。本文进一步公开了用于在治疗急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的方法中使用的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

附图说明

[0034] 本发明的新颖特征在所附权利要求中具体阐述。结合附图阅读下面的详细描述可以更好地理解本发明。需要强调的是,按照惯例,附图的各种特征不是按比例绘制的。相反,为了清楚起见,各种特征的尺寸被任意地扩大或缩小。附图中包含以下的图:

[0035] 图1示出了作为化合物1施用剂量(IV施用)的函数的恒河猴大脑中的MGLL靶标接合。

[0036] 图2A-D示出了在大鼠中单剂量化合物1之后的时程效果。单剂量化合物1(3mg/kg,

P0, n=3) 诱导了对MGLL活性(A)、大脑2-AG浓度(B)和化合物1浓度(C)的时间依赖性效应。在化合物1浓度降低至无法检测后, MGLL活性以大约2%/h的平均速率恢复(D)。示出了一个代表性实验的结果。数据表示为平均值±平均值标准误差(SEM)。

[0037] 图3A-D示出了大鼠福尔马林爪测试中单剂量化合物1的抗疼痛作用。在施用单剂量化合物1(0.1-10mg/kg, P0, 4-4.75小时, n=10)后, 化合物1浓度(A)与减少的疼痛舔爪行为(B)、大脑MGLL活性(C)和升高的大脑2-AG浓度(D)有关。示出了一个代表性实验的结果。数据表示为平均值±平均值标准误差(SEM)。通过在单向方差分析(ANOVA)后的Dunnett事后检验得到与媒介物的 $*p<0.05$ 、 $**p<0.01$ 和 $***p<0.001$ 的显著差异。

[0038] 图4A-B示出了化合物1对大鼠PBMC中的MGLL活性的抑制和大鼠血浆2-AG浓度的升高。(A) 化合物1的单剂量施用(0.03-30mg/kg, P0, 4h, n=3只大鼠每剂量)以0.07mg/kg的ED₅₀抑制大鼠PBMC中的MGLL活性。通过ABPP用氟磷酸盐-罗丹明活性探针来观察大鼠PBMC中的MGLL活性, 并通过对数转换数据的非线性回归来计算ED₅₀值。(B) 化合物1的单剂量施用(0.1-10mg/kg, P0, 4h, n=2只大鼠每剂量)使血浆2-AG浓度升高了多达7倍。绘出的数据表示平均值±平均值标准误差(SEM)。

[0039] 图5A-B示出了化合物1对人PBMC中MGLL活性的抑制。(A) 通过基于活性的蛋白质谱分析(ABPP)用氟磷酸盐-罗丹明活性探针来观察人PBMC中的MGLL活性。采用化合物1的治疗(10 μ M, 30min, 37 $^{\circ}$ C)抑制人PBMC中的MGLL活性。还观察到对羧酸酯酶1(CES1)的部分抑制。(B) 通过从来自经化合物1治疗的两个人供体5569和5392的人全血分离的PBMC裂解物中的2-AG水解来测量MGLL活性(0.3-1000nM, 30min, 37 $^{\circ}$ C, 每个供体每个浓度n=2次复制)。MGLL活性被1 μ M化合物1完全抑制, 平均IC₅₀值为47 $\pm$ 5nM(平均值±标准偏差)。绘出的数据表示平均值±标准偏差。

[0040] 图6示出了使用外源性2-AG作为底物测定PBMC中离体MGLL介导的水解, 在向人受试者口服施用化合物1后的MGLL活性的时间和剂量依赖性抑制。

[0041] 图7示出了C组(10mg QD x 14天)中第1天和第13天测量的平均化合物1血浆浓度。

[0042] 图8示出了D组(20mg QD x 14天)中第1天和第13天测量的平均化合物1血浆浓度。

[0043] 图9示出了安慰剂接受者中给药前第1天的基线PBMC介导的2-AG水解的平均百分比与给药后时间(C组和D组合并)。

[0044] 图10示出了C组(10mg QD x 14天)中给药前第1天的基线PBMC介导的2-AG水解的平均百分比与给药后时间。

[0045] 图11示出了D组(20mg QD x 14天)中给药前第1天的基线PBMC介导的2-AG水解的平均百分比与给药后时间。

具体实施方式

[0046] MGLL是一种催化大麻素受体CB₁和CB₂的内源性配体——内源性大麻素2-花生四烯酰甘油(2-AG)——水解的酶, 大麻素受体CB₁和CB₂是大麻(*Cannabis sativa*)精神活性组分 Δ^9 -四氢大麻酚(THC)的分子靶标。在啮齿类动物中, MGLL是CNS以及大多数周围组织中的主要2-AG水解酶, 并且是控制可通过CB_{1,2}发信号的2-AG的水平的主要酶。

[0047] CB₁是神经系统中主要的大麻素受体, 并且广泛分布于整个大脑中, 但在周围组织中含量较低。CB₁的激活导致THC和其他外源性大麻素(外源大麻素)在啮齿类动物和人中的

大部分神经行为作用。CB₂主要在免疫细胞上表达并介导外源大麻素的免疫抑制作用。大麻类制品(例如,**Sativex**[®])、THC(例如,**Marinol**[®])和大麻素激动剂(例如,**Cesamet**[®])直接激活大麻素受体引起对疼痛、痉挛、睡眠、食欲和恶心的治疗有益效果。

[0048] 2-AG水解产物AA是前列腺素类家族的信号传导脂质的代谢前体。MGLL有助于啮齿类动物神经系统和包括肝和肺在内的选定周围组织中AA和前列腺素类激素的产生。MGLL在小鼠中的遗传灭活或药理学灭活通过不依赖于大麻素受体的机制减少了神经变性模型中的神经炎症,表明涉及到前列腺素类激素抑制(Nomura, Science, 2011; Chen, Cell Reports, 2012; Piro, Cell Reports, 2012)。

[0049] 本公开内容至少部分涉及治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐。本文进一步公开了用于在治疗人或动物体的炎症或神经性疼痛的方法中使用的化合物1或其药学上可接受的盐。在另一个方面,本文公开了治疗有需要的患者的癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法,该方法包括向所述有需要的患者施用有效剂量的4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)或其药学上可接受的盐。本文进一步公开了用于在治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的方法中使用的化合物1或其药学上可接受的盐。在另一个方面,本文公开了用于在向受试者施用有效剂量的化合物1或其药学上可接受的盐后使受试者的血浆2-花生四烯酰甘油(2-AG)的浓度增加至少2倍至10倍的方法和医疗用途。在另一个方面,本文公开了用于使用有效剂量的化合物1或其药学上可接受的盐结合受试者的PBMC中的至少50%的MGLL的方法和医疗用途。在一些实施方案中,本文公开的方法和医疗用途需要在约1mg至约500mg范围内的有效剂量的化合物1。在一些实施方案中,本文公开的方法和医疗用途需要在约1mg至约100mg范围内的有效剂量的化合物1。在一些实施方案中,本文公开的方法和医疗用途需要在约2mg至约20mg范围内的有效剂量的化合物1。在一些实施方案中,本文公开的方法和医疗用途需要包含化合物1的组合物,该组合物使得在向受试者施用化合物1后,受试者的血浆AUC_{0-inf}为约0.2μM·hr至约2.5μM·hr。

[0050] 定义

[0051] 如说明书和所附权利要求中所用的,除非有相反的指定,否则以下术语具有下文所示的含义。

[0052] 如在本文及所附权利要求书中使用的,除非上下文另有明确说明,否则单数形式“一个”、“一种”以及“该”包括复数引用物。因此,例如,提及“一种药剂”包括多种这样的药剂,并且提及“该细胞”包括提及一个或多个细胞(或多个细胞)以及其等同物。当在本文中针对物理性质(如分子量)或化学性质(如化学式)使用范围时,旨在包括范围的所有组合和亚组合以及其中的具体实施方案。术语“约”在指代数值或数值范围时,意指所指代的数值或数值范围是实验变异性内(或统计实验误差内)的近似,因此,该数值或数值范围在所述数值或数值范围的1%至15%之间变化。术语“包含”(以及相关的术语如“包括”或“具有”或“含有”)并不旨在排除在其他某些实施方案中,例如,本文所述的任何物质组成、组合物、方法、用途或过程等的实施方案可“由所述特征组成”或“基本由所述特征组成”。

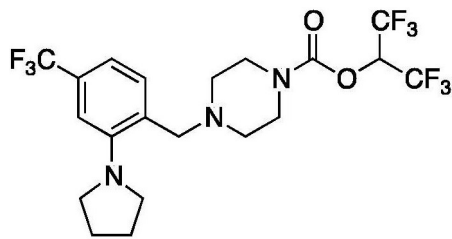
[0053] “任选的”或“任选地”意指随后描述的事件或情形可能发生或可能不发生,并意指该描述包括该事件或情形发生的情况和其没有发生的情况。例如,“任选取代的芳基”意指芳基基团被或不被取代,并意指该描述包括取代的芳基基团和没有取代的芳基基团。

[0054] 如本文所用的,“治疗”或“处理”或“减轻”或“改善”在本文中可互换使用。这些术语指获得有益的或期望的结果(包括但不限于治疗益处和/或预防益处)的途径。所谓“治疗益处”是指所治疗的潜在病症的消除或改善。并且,治疗益处通过消除或改善与潜在病症相关的一种或多种生理症状来实现,从而观察到患者的改善,尽管该患者仍受到潜在病症的折磨。对于预防益处,向处于发展特定疾病的风险中的患者或向报告疾病的一种或多种生理症状的患者施用所述组合物,即使还没有作出该疾病的诊断。

[0055] 在一些实施方案中,“受试者”和“患者”可互换使用。在一些实施方案中,“受试者”是指健康的个体。在其他实施方案中,“受试者”是指需要治疗的患者。在一些实施方案中,“受试者”是指人或动物,特别是哺乳动物。在一些实施方案中,“受试者”是指人。在一些实施方案中,“受试者”是指非人哺乳动物。

[0056] “受试者组”具有足够数目的受试者以提供相关药代动力学参数的统计学显著的平均测量。

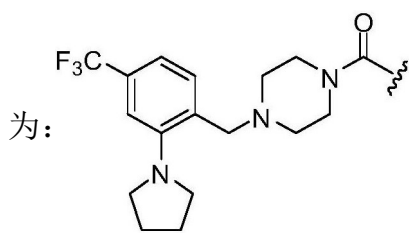
[0057] 4-(2-(吡咯烷-1-基)-4-(三氟甲基)苄基)哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯(化合物1)是一种不可逆的MGLL抑制剂。别名包括但不限于以下名称:1-哌嗪羧酸,4-[[2-(1-吡咯烷基)-4-(三氟甲基)苄基]甲基]-,2,2,2-三氟-1-(三氟甲基)乙酯;4-{[2-(吡咯烷-1-基)-4-(三氟甲基)苄基]甲基}哌嗪-1-甲酸1,1,1,3,3,3-六氟丙烷-2-基酯;以及4-{[2-(1-吡咯烷基)-4-(三氟甲基)苄基]甲基}-1-哌嗪甲酸2,2,2-三氟-1-(三氟甲基)乙酯。化合物1具有如下所示的结构:



[0058] 化合物1的制备在W0 2013/103973中公开,该申请的内容通过引用而全文并入本文。

[0059] 在一些实施方案中,化合物1的药理学上可接受的盐为盐酸盐。在进一步的实施方案中,化合物1的药理学上可接受的盐为单盐酸盐。

[0060] 在一些实施方案中,化合物1的片段与MGLL共价附接。在一些实施方案中,该片段



[0061] 方法

神经性疼痛和炎症

[0062] MGLL抑制剂在包括神经性疼痛模型在内的几种啮齿类动物疼痛模型中是有效的(Kinsey, JPET, 2009)。MGLL抑制剂还减少多种临床前模型中的疾病和炎症。在多发硬化小鼠实验性自身免疫性脑脊髓炎模型中, MGLL抑制使疾病严重性降低、防止脱髓鞘并且减少炎症(Bernal-Chico, Glia, 2015)。

[0063] 本文公开了治疗有需要的患者的疼痛或炎症的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐, 其中所述有效剂量为约1mg至约500mg。在一些实施方案中, 所述治疗方法是针对疼痛。在一些实施方案中, 所述治疗方法是针对神经性疼痛。在一些实施方案中, 所述治疗方法是针对炎症。在一些实施方案中, 所述有效剂量为约2mg至约400mg。在一些实施方案中, 所述有效剂量为约10mg至约160mg。在一些实施方案中, 所述有效剂量为约2mg至约20mg。在一些实施方案中, 所述有效剂量选自本文所述的组。在一些实施方案中, 口服施用所述有效剂量。

[0064] 本文公开了治疗有需要的患者的炎症或神经性疼痛的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐, 其中所述有效剂量为约1mg至约500mg。在一些实施方案中, 所述治疗方法是针对神经性疼痛。在一些实施方案中, 所述治疗方法是针对炎症。在一些实施方案中, 所述有效剂量为约2mg至约400mg。在一些实施方案中, 所述有效剂量为约10mg至约160mg。在一些实施方案中, 所述有效剂量为约2mg至约20mg。在一些实施方案中, 所述有效剂量选自本文所述的组。在一些实施方案中, 口服施用所述有效剂量。

[0065] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐, 其中在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少2倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少3倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少4倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少5倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少6倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少7倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少8倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少9倍。在一些实施方案中, 在施用所述有效剂量后, 所述患者的血浆2-AG的浓度增加至少10倍。在一些实施方案中, 所述有效剂量为约1mg至约500mg。在一些实施方案中, 所述有效剂量为约2mg至约400mg。在一些实施方案中, 所述有效剂量为约10mg至约160mg。在一些实施方案中, 所述有效剂量为约2mg至约20mg。在一些实施方案中, 所述有效剂量选自本文所述的组。在一些实施方案中, 所述治疗方法是针对神经性疼痛。在一些实施方案中, 所述治疗方法是针对炎症。在一些实施方案中, 口服施用所述有效剂量。

[0066] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐, 其中在施用所述有效剂量后, 化合物1的片段与来自所述患者的PBMC中的至少30%的MGLL共价附接。在一些实施方案中, 在施用所述有效剂量后, 化合物1的片段与来自所述患者的PBMC中的至少40%的MGLL共价附接。在一些实施方案中, 在施用所述有效剂量后, 化合物1的片段与来自所述患者的PBMC中的至少50%的MGLL共价附接。在一些实施方案中, 在施用所述有效剂量后, 化合物1

的片段与来自所述患者的PBMC中的至少60%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少70%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少80%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少90%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少95%的MGLL共价附接。在一些实施方案中,所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。在一些实施方案中,所述有效剂量选自本文所述的组。在一些实施方案中,所述治疗方法是针对神经性疼痛。在一些实施方案中,所述治疗方法是针对炎症。在一些实施方案中,口服施用所述有效剂量。

[0067] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.05μM·hr。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.01μM·hr。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.1μM·hr。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.2μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.3μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.4μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.5μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.6μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.7μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.8μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少0.9μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少1.0μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少1.5μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少2.0μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的血浆AUC_{0-inf}为至少2.5μM·hr。在一些实施方案中,所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。在一些实施方案中,所述有效剂量选自本文所述的组。在一些实施方案中,所述治疗方法是针对神经性疼痛。在一些实施方案中,所述治疗方法是针对炎症。在一些实施方案中,口服施用所述有效剂量。

[0068] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.05μM·hr。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.01μM·hr。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.1μM·hr。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.2μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.3μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.4μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.5μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.6μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.7μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.8μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少0.9μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少1.0μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少1.5μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少2.0μM·hr。在一些实施方案中,在施用所述有效剂量后,化合物1的稳态血浆AUC_{0-inf}为至少2.5μM·hr。在一些实施方案中,所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。在一些实施方案中,所述有效剂量选自本文所述的组。在一些实施方案中,所述治疗方法是针对神经性疼痛。在一些实施方案中,所述治疗方法是针对炎症。在一些实施方案中,口服施用所述有效剂量。

[0069] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中在施用所述有效剂量后:(a) 所述患者的血浆2-AG的浓度增加至少2倍;并且(b) 化合物1的片段与来自所述患者的PBMC中的至少30%的MGLL共价衔接。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少3倍。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少4倍。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少5倍。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少6倍。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少7倍。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少8倍。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少9倍。在一些实施方案中,在施用所述有效剂量后,所述患者的血浆2-AG的浓度增加至少10倍。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所

述患者的PBMC中的至少40%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少50%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少60%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少70%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少80%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少90%的MGLL共价附接。在一些实施方案中,在施用所述有效剂量后,化合物1的片段与来自所述患者的PBMC中的至少95%的MGLL共价附接。在一些实施方案中,所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。在一些实施方案中,所述有效剂量选自本文所述的组。在一些实施方案中,所述治疗方法是针对神经性疼痛。在一些实施方案中,所述治疗方法是针对炎症。在一些实施方案中,口服施用所述有效剂量。

[0070] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含有效剂量的化合物1或其药学上可接受的盐的组合物,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述治疗方法是针对神经性疼痛。在一些实施方案中,所述治疗方法是针对炎症。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。在一些实施方案中,所述有效剂量选自本文所述的组。在一些实施方案中,口服施用所述组合物。

[0071] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.01\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.1\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用提供至少 $0.2\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,所述组合物的施用提供至少 $0.3\mu\text{M} \cdot \text{hr}$ 、至少 $0.4\mu\text{M} \cdot \text{hr}$ 、至少 $0.5\mu\text{M} \cdot \text{hr}$ 、至少 $0.6\mu\text{M} \cdot \text{hr}$ 、至少 $0.7\mu\text{M} \cdot \text{hr}$ 、至少 $0.8\mu\text{M} \cdot \text{hr}$ 、至少 $0.9\mu\text{M} \cdot \text{hr}$ 、至少 $1.0\mu\text{M} \cdot \text{hr}$ 、至少 $1.1\mu\text{M} \cdot \text{hr}$ 、至少 $1.2\mu\text{M} \cdot \text{hr}$ 、至少 $1.3\mu\text{M} \cdot \text{hr}$ 、至少 $1.4\mu\text{M} \cdot \text{hr}$ 、至少 $1.5\mu\text{M} \cdot \text{hr}$ 、至少 $1.6\mu\text{M} \cdot \text{hr}$ 、至少 $1.7\mu\text{M} \cdot \text{hr}$ 、至少 $1.8\mu\text{M} \cdot \text{hr}$ 、至少 $1.9\mu\text{M} \cdot \text{hr}$ 、至少 $2.0\mu\text{M} \cdot \text{hr}$ 、至少 $2.1\mu\text{M} \cdot \text{hr}$ 、至少 $2.2\mu\text{M} \cdot \text{hr}$ 、至少 $2.3\mu\text{M} \cdot \text{hr}$ 、至少 $2.4\mu\text{M} \cdot \text{hr}$ 、至少 $2.5\mu\text{M} \cdot \text{hr}$ 、至少 $2.6\mu\text{M} \cdot \text{hr}$ 、至少 $2.7\mu\text{M} \cdot \text{hr}$ 、至少 $2.8\mu\text{M} \cdot \text{hr}$ 、至少 $2.9\mu\text{M} \cdot \text{hr}$ 或至少 $3.0\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,所述组合物包含约1mg至约500mg的化合物1或其药学上可接受

的盐。在一些实施方案中,所述组合物包含约2mg至约400mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约10mg至约160mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约2mg至约20mg的化合物1或其药学上可接受的盐。在一些实施方案中,口服施用所述组合物。

[0072] 本文还描述了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用将所述患者的血浆2-AG的浓度增加至少2倍。在一些实施方案中,所述组合物的施用将所述患者的血浆2-AG的浓度增加至少3倍、至少4倍、至少5倍、至少6倍、至少7倍、至少8倍、至少9倍或至少10倍。在一些实施方案中,所述组合物包含约1mg至约500mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约2mg至约400mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约10mg至约160mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约2mg至约20mg的化合物1或其药学上可接受的盐。在一些实施方案中,口服施用所述组合物。

[0073] 本文还公开了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价附接。在一些实施方案中,所述组合物的施用使得来自所述患者的PBMC中的至少40%、至少50%、至少60%、至少70%、至少80%、至少90%或至少95%的MGLL与化合物1的片段共价附接。在一些实施方案中,所述组合物包含约1mg至约500mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约2mg至约400mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约10mg至约160mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述组合物包含约2mg至约20mg的化合物1或其药学上可接受的盐。在一些实施方案中,口服施用所述组合物。

[0074] 本文还描述了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用(a)将所述患者的血浆2-AG的浓度增加至少2倍,并且(b)使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价附接。

[0075] 本文还描述了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用(a)提供至少 $0.05\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$; (b)将所述患者的血浆2-AG的浓度增加至少2倍;并且(c)使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价附接。本文还描述了治疗有需要的患者的炎症或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用(a)提供至少 $0.01\mu\text{M} \cdot \text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$; (b)将所述患者的血浆2-AG的浓度增加至少2倍;并且(c)使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价附接。本文还描述了治疗有需要的患者的炎症

或神经性疼痛的方法,该方法包括向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物,其中所述组合物的施用(a)提供至少 $0.2\mu\text{M}\cdot\text{hr}$ 的血浆 $\text{AUC}_{0-\text{inf}}$; (b) 将所述患者的血浆2-AG的浓度增加至少2倍;并且(c)使得来自所述患者的PBMC中的至少30%的MGLL与化合物1的片段共价附接。

急性疼痛、炎性疼痛、癌症疼痛和由周围神经病变引起的疼痛

[0076] MGLL抑制剂已经在几种啮齿类动物疼痛模型中显示出功效,该模型包括急性疼痛模型(Long, Nature Chemical Biology, 2009)、炎性疼痛模型(Anderson, Neuropharmacology, 2013)、癌症疼痛模型(Khasabova, Pharmacology Research, 2011)和由化疗诱导的周围神经病变引起的疼痛模型(Guindon, Pharmacology Research, 2013)。

[0077] 在一些实施方案中,本文公开了治疗有需要的患者的急性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的急性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。在一些实施方案中,本文公开了治疗有需要的患者的炎性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的炎性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。在一些实施方案中,本文公开了治疗有需要的患者的癌症疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的癌症疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。在一些实施方案中,本文公开了治疗有需要的患者的由周围神经病变引起的疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的由周围神经病变引起的疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗急性疼痛的方法中使用的化合物1或其药学上可接受的盐,该方法任选地包括施用约1mg至约100mg的剂量。

中枢性疼痛

[0078] 中枢性疼痛是由中枢神经系统的损伤或功能障碍(例如,中风后遗症、多发性硬化、视神经脊髓炎、特发性炎性横贯性脊髓炎、脊髓损伤、臂-桡疼痛综合征(brachial-radial pain syndrome)和中枢性颅面疼痛)引起的神经性疼痛。外源大麻素已在与多发性硬化相关的中枢性疼痛中显示出活性。使用含有CB₁激动剂 δ -9-四氢大麻酚和大麻二醇(另一种大麻属衍生的醇)的口腔粘膜喷雾剂THC/CBD进行的MS和中枢性疼痛的4周随机化双盲安慰剂对照平行组试验显示,活性剂在降低疼痛(NRS-11)和睡眠障碍的平均强度方面优于安慰剂(Rog, Neurology, 2005, 65 (6), 812-9)。采用两阶段设计,在更大的患有中枢性神经性疼痛的MS患者组中研究了同一THC/CBD制品;在该研究的第二阶段,治疗失败的时间(主要终点)在统计学上有利于THC/CBD,因为其改善了疼痛NRS-11和睡眠质量(Langford, J Neurol, 2013, 260 (4), 984-97)。此外,一种在结构上与THC相关的合成CB₁激动剂——大麻隆显示出对MS诱导的中枢性神经性疼痛的效力(Turcotte, Pain Med, 2015, 16 (1), 149-

59)。在中枢性疼痛中对外源大麻素的一些研究已经显示出活性,这表明MGLL抑制剂也可能具有治疗中枢性疼痛的效力。

[0079] 在一些实施方案中,本文公开了治疗有需要的患者的中枢性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的中枢性疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗中枢性疼痛的方法中使用的化合物1或其药学上可接受的盐,该方法任选地包括施用约1mg至约100mg的剂量。

纤维肌痛

[0080] 纤维肌痛(FM)是一种常见的慢性特发性病况,以弥漫性身体疼痛和存在压力异常性疼痛为特征。度洛西汀和普瑞巴林被特别标记用于治疗FM中的疼痛,而三环类抗抑郁药如阿米替林,虽然没有被特别标记用于FM治疗,但是是一线药剂。没有对FM的明确的病理学理解,并且没有经验证的临床前模型。然而,在FM中对外源大麻素的一些研究已经显示出活性,这表明MGLL抑制剂也可能具有治疗FM的功效。疼痛(例如,NRS-11,疼痛VAS)的测量和衡量受FM影响的一些日常活动限制的纤维肌痛影响问卷(FIQ)已显示出药物在FM临床试验中的活性(Burckhardt, J Rheumatol, 1991, 18 (5), 728-33; Mease, J Rheumatol, 2008, 35 (3), 502-14)。进行了对是大麻属使用者和非使用者的西班牙FM患者的调查,以鉴别大麻属对一系列疾病症状如疼痛、僵硬、幸福感、放松和嗜睡的影响;常见到对于疼痛、睡眠障碍、僵硬情绪障碍和焦虑的感官缓解(Fiz, PLoS One, 2011, 6 (4), e18440)。在8周40名患者的研究中,与安慰剂相比,外源大麻素大麻隆改善了经10cm VAS测量的疼痛,并改善了FIQ焦虑域和FIQ总得分(Skrabek, J Pain, 2008, 9 (2), 164-73)。在31名患者的研究中,与阿米替林相比,大麻隆改善了睡眠指数(失眠严重性指数)并且经疼痛测量(McGill疼痛问卷)和FIQ判断为非劣性(Ware, Anesth Analg, 2010, 110 (2), 604-10)。

[0081] 在一些实施方案中,本文公开了治疗有需要的患者的纤维肌痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的纤维肌痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗纤维肌痛的方法中使用的化合物1或其药学上可接受的盐,该方法任选地包括施用约1mg至约100mg的剂量。

偏头痛

[0082] 偏头痛是头部和面部疼痛的常见发作性病症。偏头痛发作可以用NSAID、醋氨酚、多种曲坦类药物(例如,舒马曲坦)和止吐药来急性治疗,但一些偏头痛患者的疼痛对现有的治疗选项无反应。数据表明,内源性大麻素通路可能与偏头痛相关。在患有慢性偏头痛和可能的止痛药过度使用性头痛的患者中,相比于健康对照,CSF样品显示出较高水平的内源性大麻素十六酰胺乙醇和较低水平的花生四烯酸乙醇胺(anandamide) (Sarchielli, Neuropsychopharmacology, 2007, 32 (6), 1384-90)。此外,对在医疗大麻诊所就诊的初步诊断为偏头痛性头痛的患者的回顾性病例综述发现在开始大麻治疗后偏头痛性头痛的频率下降(Rhyne, Pharmacotherapy, 2016),表明MGLL抑制剂也可能具有治疗偏头痛的功效。

[0083] 在一些实施方案中,本文公开了治疗有需要的患者的偏头痛的方法,该方法包括

向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中，公开了治疗有需要的患者的偏头痛的方法，该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐，其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗偏头痛的方法中使用的化合物1或其药学上可接受的盐，该方法任选地包括施用约1mg至约100mg的剂量。

镰状细胞病血管阻塞性疼痛危象

[0084] 血管阻塞性疼痛危象被认为是由镰状细胞病 (SCD) 患者中伴有微毛细血管阻塞和缺血性疼痛的红血细胞 (RBC) 流变学改变而引起，该镰状细胞病是一种由成年血红蛋白 β 基因的突变引起的遗传性病况。通常用口服或静脉内阿片样止痛药治疗SCD中的血管阻塞性疼痛危象；慢性阿片样物质可用于一半的成年患者。神经性疼痛可在更大的年龄中发生，表现为痛觉过敏和异常性疼痛；有时将针对慢性神经性疼痛的药物用于这些患者。对伦敦的SCD患者的一项调查发现，36%的问卷调查对象在去年使用了大麻属来缓解与SCD有关的症状(主要是疼痛) (Howard, Br J Haematol, 2005, 131 (1), 123-8)。此外，表达人镰状血红蛋白的小鼠中的疼痛相关行为和神经化学改变被大麻素受体激动剂CP-55940显著改善 (Kohli, Blood, 2010, 116 (3), 456-65)。该数据表明，MGLL抑制剂是用于治疗SCD中的血管阻塞性疼痛危象的潜在治疗剂。

[0085] 在一些实施方案中，本文公开了治疗有需要的患者的镰状细胞病血管阻塞性疼痛危象的方法，该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中，公开了治疗有需要的患者的镰状细胞病血管阻塞性疼痛危象的方法，该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐，其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗镰状细胞病血管阻塞性疼痛危象的方法中使用的化合物1或其药学上可接受的盐，该方法任选地包括施用约1mg至约100mg的剂量。

多发性硬化的对症治疗

[0086] 几乎所有亚型的所有多发性硬化 (MS) 患者都有痉挛、疼痛、睡眠障碍、膀胱功能障碍和疲劳中的一种或多种症状。疾病改善疗法不会改善症状。痉挛影响超过80%的MS患者；34%的MS患者具有中度、重度或完全的痉挛。严重的痉挛与照护的花费和水平有关，并与MS的生活质量独立相关。两篇最近的综述支持使用外源大麻素治疗MS痉挛和疼痛 (Whiting, JAMA, 2015, 313 (24), 2456-2473; Hill, JAMA, 2015, 313 (24), 2474-83)。

[0087] 外源大麻素制品是针对与多发性硬化有关的痉挛的经批准的治疗。显示Sativex (CB₁激动剂THC与另一种大麻属植物衍生的醇——大麻二醇的口腔粘膜喷雾混合物) 减少了自我报告的痉挛相关的症状。在采用随机抽取设计的对Sativex的一项关键性试验中，存在采用连续Sativex在痉挛频率、痉挛下的睡眠中断、受试者对变化的总体印象、照护者对变化的总体印象以及医生对变化的总体印象方面的改善。其他临床试验显示了多种外源大麻素在多发性硬化引起的痉挛中的活性 (Zajicek, Lancet, 2003, 362 (9395), 1517-26; Collin, Eur J Neurol, 2007, 14 (3), 290-6; Collin, Neurol Res, 2010, 32 (5), 451-9)。这些平行组研究例示了可用于显示MGLL有益于MS中的痉挛的临床试验设计和终点。

[0088] 在一些实施方案中，本文公开了治疗有需要的患者的与多发性硬化相关的痉挛或疼痛的方法，该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受

的盐。在一些实施方案中,公开了治疗有需要的患者的与多发性硬化相关的痉挛或疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗与多发性硬化相关的痉挛或疼痛的方法中使用的化合物1或其药学上可接受的盐,该方法任选地包括施用约1mg至约100mg的剂量。

功能性胸痛

[0089] 功能性胸痛有时称为非GERD(非心源性胸痛),是一种在胸部感觉到上部GI结构的不适的功能性胃肠道病症。除了消耗医疗资源来排除其他可治疗的病况之外,功能性胸痛还给患者带来痛苦。可用三环类抗抑郁药或血清素去甲肾上腺素再摄取抑制剂治疗功能性胸痛,但并非所有患者都有反应。在患有由于GI超敏反应引起的综合征——功能性胸痛的患者中,在带安慰剂对照的4周研究中,外源大麻素屈大麻酚改善了胸痛症状并提高了食管气囊膨胀的感觉阈值(Malik, Dis Esophagus, 2016, 网上公布.DOI:10.1111/dote.12455),表明MGLL抑制剂也可能具有治疗功能性胸痛的功效。

[0090] 在一些实施方案中,本文公开了治疗有需要的患者的功能性胸痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的功能性胸痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗功能性胸痛的方法中使用的化合物1或其药学上可接受的盐,该方法任选地包括施用约1mg至约100mg的剂量。

类风湿性关节炎和骨关节炎

[0091] 发现CB₁和CB₂受体存在于类风湿性关节炎(RA)和骨关节炎(OA)患者的滑液中。在RA和OA患者的滑液中鉴别出内源性大麻素花生四烯酸乙醇胺和2-AG,但在正常志愿者中未鉴别到(Richardson, Arthritis Res Ther, 2008, 10(2), R43)。此外,nabiximol(THC/CBD口腔粘膜喷雾剂)的小型RA患者试验显示休息时的运动疼痛改善、睡眠改善以及28个关节的标准RA疾病活动评分(DAS28)的改善(Blake, Rheumatology (Oxford), 2006, 45(1), 50-2)。这些数据预测MGLL可能是治疗RA和OA中的疼痛和炎症的重要治疗靶标。

[0092] 在一些实施方案中,本文公开了治疗有需要的患者的类风湿性关节炎或骨关节炎的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的类风湿性关节炎或骨关节炎的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。在一些实施方案中,本文公开了治疗有需要的患者的类风湿性关节炎疼痛或骨关节炎疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的类风湿性关节炎疼痛或骨关节炎疼痛的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗类风湿性关节炎或骨关节炎的方法中使用的化合物1或其药学上可接受的盐,该方法任选地包括施用约1mg至约100mg的剂量。

阿尔茨海默病

[0093] 阿尔茨海默病(AD)是痴呆的最常见病因,影响了美国约530万人。躁动和攻击是将

痴呆患者收容入院的危险因素。外源大麻素屈大麻酚改善了厌食并减少了AD患者的躁动 (Volicer, Int J Geriatr Psychiatry, 1997, 12 (9), 913-9), 并且减少了AD患者的夜间躁动 (Walther, J Clin Psychopharmacol, 2011, 31 (2), 256-8)。可以在患有痴呆和躁动的选定AD患者的平行组或交叉研究中对MGLL抑制剂进行测试。作为实例, CIT-AD试验测量了随机化至心理干预外加安慰剂或西酞普兰持续9周的患者躁动的 (Porsteinsson, JAMA, 2014, 311 (7), 682-91)。

[0094] 在一些实施方案中, 本文公开了治疗有需要的患者的与阿尔茨海默病相关的躁动或攻击的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中, 公开了治疗有需要的患者的与阿尔茨海默病相关的躁动或攻击的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐, 其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗与阿尔茨海默病相关的躁动或攻击的方法中使用的化合物1或其药学上可接受的盐, 该方法任选地包括施用约1mg至约100mg的剂量。

功能性消化不良

[0095] 功能性消化不良 (FD) 是临床实践中遇到的最常见的胃肠道病症之一。已经提出了引发FD症状产生的几种病理生理学机制, 包括由于中枢或周围致敏引起的内脏超敏反应、低度炎症状态、胃肠激素分泌改变、遗传易感性以及胃排空或容受性异常。通过施用CB₁受体拮抗剂利莫那班来抑制健康人的胃容受性 (Ameloot, Aliment Pharmacol Ther, 2010, 31 (10), 1123-31)。此外, 研究支持FD患者的内源性大麻素系统功能被改变的假设; 因此, 推断通过提高2-AG、进而激活CB₁受体而导致的MGLL抑制将会增加胃容受性并减轻功能性消化不良的症状 (Ly, Psychother Psychosom, 2015, 84 (3), 149-58)。

[0096] 在一些实施方案中, 本文公开了治疗有需要的患者的功能性消化不良的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中, 公开了治疗有需要的患者的功能性消化不良的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐, 其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗功能性消化不良的方法中使用的化合物1或其药学上可接受的盐, 该方法任选地包括施用约1mg至约100mg的剂量。

炎性肠病

[0097] 炎性肠病 (IBD) 包括全部或部分消化道的慢性炎症。IBD主要包括溃疡性结肠炎和克罗恩病。两者通常均涉及严重腹泻、疼痛、疲劳和体重减轻。IBD可使人虚弱, 并且有时会导致危及生命的并发症。MGLL抑制在IBD的小鼠模型中是保护性的 (Alhouayek, FASEB, 2011, 2711-2721)。

[0098] 在一些实施方案中, 本文公开了治疗有需要的患者的炎性肠病的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中, 公开了治疗有需要的患者的炎性肠病的方法, 该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐, 其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗炎性肠病的方法中使用的化合物1或其药学上可接受的盐, 该方法任选地包括施用约1mg至约100mg的剂量。

骨骼肌挫伤

[0099] 骨骼肌挫伤指示对肌肉的直接的钝性压缩力。挫伤是最常见的运动相关损伤中的一种。挫伤的严重性为从简单的皮肤挫伤到肌肉和骨头挫伤到内脏挫伤。MGLL抑制在大鼠骨骼肌挫伤模型中显示出抗炎作用(Jiang, European Journal of Pharmacology, 2015, 网上公布.dx.doi.org/10.1016)。

[0100] 在一些实施方案中,本文公开了治疗有需要的患者的骨骼肌挫伤的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐。在一些实施方案中,公开了治疗有需要的患者的骨骼肌挫伤的方法,该方法包括向所述有需要的患者施用有效剂量的化合物1或其药学上可接受的盐,其中所述有效剂量为约1mg至约100mg。本文还公开了用于在治疗人或动物体的骨骼肌挫伤的方法中使用的化合物1或其药学上可接受的盐,该方法任选地包括施用约1mg至约100mg的剂量。

其他方法

[0101] 本文公开了对有需要的患者的炎症或神经性疼痛治疗的治疗功效进行优化的方法,该方法包括(a)向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物;(b)测量所述患者的血浆2-AG的浓度;以及(c)如通过血浆2-AG的浓度所指示的,施用增加或减少量的化合物1。本文还公开了用于在对患者的炎症或神经性疼痛治疗的治疗功效进行优化的方法中使用的化合物1或其药学上可接受的盐,所述方法包括(a)向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物;(b)测量所述患者的血浆2-AG的浓度;以及(c)如通过血浆2-AG的浓度所指示的,施用增加或减少量的化合物1。

[0102] 本文公开了对有需要的患者的炎症或神经性疼痛治疗的治疗功效进行优化的方法,该方法包括(a)向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物;(b)测量来自所述患者的PBMC中与化合物1的片段共价附接的MGLL的百分比;以及(c)如通过血浆中与化合物1的片段共价附接的MGLL的百分比所指示的,施用增加或减少量的化合物1。本文还公开了用于在对患者的炎症或神经性疼痛治疗的治疗功效进行优化的方法中使用的化合物1或其药学上可接受的盐,所述方法包括(a)向所述有需要的患者施用包含化合物1或其药学上可接受的盐的组合物;(b)测量来自所述患者的PBMC中与化合物1的片段共价附接的MGLL的百分比;以及(c)如通过血浆中与化合物1的片段共价附接的MGLL的百分比所指示的,施用增加或减少量的化合物1。

[0103] 本文公开了使用有效剂量的化合物1或其药学上可接受的盐增加受试者的血浆2-AG的浓度的方法,其中受试者的血浆2-AG的浓度增加至少2倍。本文还公开了用于在通过施用有效剂量的化合物1或其药学上可接受的盐来增加受试者的血浆2-AG浓度的治疗方法中使用的化合物1或其药学上可接受的盐,其中受试者的血浆2-AG的浓度增加至少2倍。在一些实施方案中,受试者的血浆2-AG的浓度增加至少3倍、至少4倍、至少5倍、至少6倍、至少7倍、至少8倍、至少9倍或至少10倍。在一些实施方案中,所述有效剂量为约1mg至约500mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述有效剂量为约2mg至约400mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述有效剂量为约10mg至约160mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述有效剂量为约2mg至约20mg的化合物1或其药学上可接受的盐。在一些实施方案中,口服施用所述有效剂量。

[0104] 本文还公开了在向受试者施用有效剂量的化合物1或其药学上可接受的盐后使MGLL与化合物1在所述受试者的PBMC中结合的方法,其中化合物1的片段与PBMC中的至少

30%的MGLL共价衔接。本文还公开了用于在本文公开的任一种治疗方法中使用的化合物1或其药学上可接受的盐,其中在向受试者施用有效剂量的化合物1或其药学上可接受的盐后,化合物1的片段与所述受试者的PBMC中的至少30%的MGLL共价衔接。在一些实施方案中,化合物1的片段与PBMC中的至少40%、至少50%、至少60%、至少70%、至少80%、至少90%或至少95%的MGLL共价衔接。在一些实施方案中,所述有效剂量为约1mg至约500mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述有效剂量为约2mg至约400mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述有效剂量为约10mg至约160mg的化合物1或其药学上可接受的盐。在一些实施方案中,所述有效剂量为约2mg至约20mg的化合物1或其药学上可接受的盐。在一些实施方案中,口服施用所述有效剂量。

剂量和血浆AUC

[0105] 在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg、约2mg、约3mg、约4mg、约5mg、约6mg、约7mg、约8mg、约9mg、约10mg、约11mg、约12mg、约13mg、约14mg、约15mg、约16mg、约17mg、约18mg、约19mg、约20mg、约21mg、约22mg、约23mg、约24mg、约25mg、约26mg、约27mg、约28mg、约29mg、约30mg、约31mg、约32mg、约33mg、约34mg、约35mg、约36mg、约37mg、约38mg、约39mg、约40mg、约41mg、约42mg、约43mg、约44mg、约45mg、约46mg、约47mg、约48mg、约49mg、约50mg、约55mg、约60mg、约65mg、约70mg、约75mg、约80mg、约85mg、约90mg、约95mg、约100mg、约110mg、约120mg、约130mg、约140mg、约150mg、约160mg、约170mg、约180mg、约190mg、约200mg、约210mg、约220mg、约230mg、约240mg、约250mg、约260mg、约270mg、约280mg、约290mg、约300mg、约310mg、约320mg、约330mg、约340mg、约350mg、约360mg、约370mg、约380mg、约390mg、约400mg、约410mg、约420mg、约430mg、约440mg、约450mg、约460mg、约470mg、约480mg、约490mg或约500mg,包括其中的增量。

[0106] 在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约500mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约450mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约400mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约350mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约300mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约250mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约200mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约150mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约100mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约50mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约25mg。在一些实施方案中,在本文公开的方法和医疗用途中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约15mg。在一些实施方案中,在本文公开的方

次。

[0108] 在一些实施方案中,在施用化合物1或其药学上可接受的盐后,从受试者收集血液样品。在一些实施方案中,分析所述血液样品的化合物1定量。

[illegible]

[0110] 在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的血浆AUC_{0-inf}为约0.01μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的血浆AUC_{0-inf}为约0.05μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的血浆AUC_{0-inf}为约0.1μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的血浆AUC_{0-inf}为约0.15μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的血浆AUC_{0-inf}为约0.2μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得

[illegible]

[0111] 在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为至少0.05μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为至少0.01μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为至少0.1μM·hr。

[illegible]

[0112] 在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.01μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.05μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.1μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.15μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.2μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.3μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.4μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}为约0.5μM·hr至约3.0μM·hr。在一些实施方案中,化合物1或其药学上可接受的盐向受试者的施用使得化合物1的稳态血浆AUC_{0-inf}

[illegible]

[0113] 在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生至少 $0.05\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生至少 $0.01\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生至少 $0.1\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生至少 $0.2\mu\text{M} \cdot \text{hr}$ 的化合物1平均血

[illegible]

[0114] 在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.01\mu\text{M}\cdot\text{hr}$ 至约 $3.0\mu\text{M}\cdot\text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.05\mu\text{M}\cdot\text{hr}$ 至约 $3.0\mu\text{M}\cdot\text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.1\mu\text{M}\cdot\text{hr}$ 至约 $3.0\mu\text{M}\cdot\text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产

[illegible]

盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.2\mu\text{M} \cdot \text{hr}$ 至约 $2.0\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.3\mu\text{M} \cdot \text{hr}$ 至约 $2.0\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.4\mu\text{M} \cdot \text{hr}$ 至约 $2.0\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.5\mu\text{M} \cdot \text{hr}$ 至约 $2.0\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.7\mu\text{M} \cdot \text{hr}$ 至约 $2.0\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $1.0\mu\text{M} \cdot \text{hr}$ 至约 $2.0\mu\text{M} \cdot \text{hr}$ 的化合物1平均血浆 $\text{AUC}_{0-\text{inf}}$ 。

[0115] 在一些实施方案中,在向受试者施用化合物1后,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用在人受试者组中产生约 $0.01\mu\text{M} \cdot \text{hr}$ 、 $0.05\mu\text{M} \cdot \text{hr}$ 、 $0.1\mu\text{M} \cdot \text{hr}$ 、 $0.15\mu\text{M} \cdot \text{hr}$ 、约 $0.2\mu\text{M} \cdot \text{hr}$ 、约 $0.3\mu\text{M} \cdot \text{hr}$ 、约 $0.4\mu\text{M} \cdot \text{hr}$ 、约 $0.5\mu\text{M} \cdot \text{hr}$ 、约 $0.6\mu\text{M} \cdot \text{hr}$ 、约 $0.7\mu\text{M} \cdot \text{hr}$ 、约 $0.8\mu\text{M} \cdot \text{hr}$ 、约 $0.9\mu\text{M} \cdot \text{hr}$ 、约 $1.0\mu\text{M} \cdot \text{hr}$ 、约 $1.1\mu\text{M} \cdot \text{hr}$ 、约 $1.2\mu\text{M} \cdot \text{hr}$ 、约 $1.3\mu\text{M} \cdot \text{hr}$ 、约 $1.4\mu\text{M} \cdot \text{hr}$ 、约 $1.5\mu\text{M} \cdot \text{hr}$ 、约 $1.6\mu\text{M} \cdot \text{hr}$ 、约 $1.7\mu\text{M} \cdot \text{hr}$ 、约 $1.8\mu\text{M} \cdot \text{hr}$ 、约 $1.9\mu\text{M} \cdot \text{hr}$ 、约 $2.0\mu\text{M} \cdot \text{hr}$ 、约 $2.1\mu\text{M} \cdot \text{hr}$ 、约 $2.2\mu\text{M} \cdot \text{hr}$ 、约 $2.3\mu\text{M} \cdot \text{hr}$ 、约 $2.4\mu\text{M} \cdot \text{hr}$ 、约 $2.5\mu\text{M} \cdot \text{hr}$ 、约 $2.6\mu\text{M} \cdot \text{hr}$ 、约 $2.7\mu\text{M} \cdot \text{hr}$ 、约 $2.8\mu\text{M} \cdot \text{hr}$ 、约 $2.9\mu\text{M} \cdot \text{hr}$ 、约 $3.0\mu\text{M} \cdot \text{hr}$ 、约 $3.1\mu\text{M} \cdot \text{hr}$ 、约 $3.2\mu\text{M} \cdot \text{hr}$ 、约 $3.3\mu\text{M} \cdot \text{hr}$ 、约 $3.4\mu\text{M} \cdot \text{hr}$ 、约 $3.5\mu\text{M} \cdot \text{hr}$ 、约 $3.6\mu\text{M} \cdot \text{hr}$ 、约 $3.7\mu\text{M} \cdot \text{hr}$ 、约 $3.8\mu\text{M} \cdot \text{hr}$ 、约 $3.9\mu\text{M} \cdot \text{hr}$ 或约 $4.0\mu\text{M} \cdot \text{hr}$ 的平均血浆 $\text{AUC}_{0-\text{inf}}$ 。

[0116] 在一些实施方案中,在施用化合物1或其药学上可接受的盐后从受试者收集尿液。在一些实施方案中,分析了尿液的尿液化合物1定量和尿液排泄特征。在进一步的实施方案中,分析了尿液的定性代谢物特征。

[0117] 在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用对受试者或患者的心境状态产生较小影响或没有影响。在一些实施方案中,采用心境状态量表的较短版本(30项)(POMS简短形式)来评估受试者或患者的心境在给药前后的波动。在一些实施方案中,将POMS数据用于评估对心境的潜在的化合物1剂量相关影响。

[0118] 在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用对受试者或患者的认知功能产生较小影响或没有影响。在一些实施方案中,使用一系列标准化和经验证的计算机化测试(Cogstate系列)来评价对认知功能的影响。该系列包括以下测试:格罗顿迷宫学习测试(Groton Maze Learning Test, GMLT)、检测(DET)、识别(IDN)、一卡学习(OCL)和ONB(One Back)任务。在一些实施方案中,受试者或患者在给药前以及在给药后以方案指定的间隔进行该系列测试,以评价对认知、问题解决/推理、处理速度、注意力/警觉和视觉识别记忆的潜在化合物1剂量相关影响。

[0119] 在一些实施方案中,化合物1或其药学上可接受的盐在本文公开的方法和医疗用途中的施用对受试者或患者的皮肤热阈值(CTT)产生轻微影响或没有影响。

[0120] 靶标接合

[0121] 在一些实施方案中,在施用化合物1或其药学上可接受的盐后,来自受试者的血

液样品测量化合物1的血浆浓度。

[0122] 在一些实施方案中,评价了来自受试者的血液样品的MGLL活性。在一些实施方案中,通过测量血浆2-AG浓度来评价MGLL活性。2-AG为内源性MGLL底物。临床前物种中MGLL的体内抑制与2-AG浓度(大脑中以及外周血中)的增加有关。在一些实施方案中,采用体外测定测量血浆2-AG浓度。在一些实施方案中,采用适合于目的的质谱测定来测量血浆2-AG浓度。在一些实施方案中,从被收集用于评价化合物1血浆浓度的相同血液样品测量血浆2-AG浓度。

[0123] 由于已知人体中血浆2-AG浓度经历昼夜波动[Hanlon等人,“Circadian rhythm of circulating levels of the endocannabinoid 2-arachidonoylglycerol”, J.Clin.Endocrinol.Metab.100:220-226, (2015)],因此将来自化合物1盐酸盐接受者和安慰剂接受者的血浆2-AG数据用于评价化合物1盐酸盐的剂量相关影响。在一些实施方案中,未治疗的受试者的平均血浆2-AG浓度为约~1.8ng/mL (~4.8nM)。在一些实施方案中,未治疗的受试者的血浆2-AG浓度在约0.5ng/mL至约5ng/mL范围内。

[0124] 在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少2倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少3倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少4倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少5倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少6倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少7倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少8倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少9倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加至少10倍。

[0125] 在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约2倍至约10倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约2倍至约3倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约2倍至约4倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约2倍至约5倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约2倍至约6倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约2倍至约7倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约5倍至约7倍。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度增加约5倍至约10倍。

[0126] 在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为约1ng/mL至约10ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为约1.5ng/mL至约15ng/mL。在一些实施方案

中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为约2.6ng/mL至约15ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为约3.0ng/mL至约18.0ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为约4.0ng/mL至约15ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为约5.0ng/mL至约15ng/mL。

[0127] 在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少2.6ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约5.4ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约7.2ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约9.0ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约10.8ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约12.6ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约14.4ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约16.2ng/mL。在一些实施方案中,在向受试者施用化合物1或其药学上可接受的盐后,受试者的血浆2-AG浓度为至少约18.0ng/mL。

[0128] 在一些实施方案中,测定了残留血浆(即,研究完成并揭盲后)中一种或多种其他内源脂质介体(例如,其他单酰甘油脂质和另一种主要的内源性大麻素并且是FAAH的主要底物——花生四烯酸乙醇胺(AEA))的存在。

[0129] 在一些实施方案中,评价了来自受试者的血液样品的外周血单核细胞(PBMC)的MGLL活性。先前的体外研究已证明从健康人供体制备的PBMC中存在可测量的MGLL活性。在一些实施方案中,使用基于活性的蛋白质谱分析(ABPP)电泳技术或通过基于底物的测定容易地将外源添加的MGLL抑制剂在这些PBMC制品中的药理学活性定量。在一些实施方案中,在施用研究药物之前,以及在施用研究药物后以指定的时间间隔采用适合于目的的底物测定在从受试者收集的PBMC中测量PBMC中的MGLL靶标接合。在一些实施方案中,评价化合物1对PBMC MGLL活性的剂量和暴露相关影响。在一些实施方案中,使用基于质谱法的底物测定来评价PBMC中的MGLL活性。

[0130] 在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少30%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少40%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少50%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少55%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少60%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少65%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少70%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受

试者的PBMC中的至少75%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少80%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少85%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少90%的MGLL共价附接。在一些实施方案中,在向受试者施用化合物1后,化合物1的片段与来自受试者的PBMC中的至少95%的MGLL共价附接。在一些实施方案中,采用体外测定对与受试者的PBMC中的MGLL共价附接的化合物1片段进行测量。

[0131] 在一些实施方案中,还使用ABPP技术测定残留PBMC部分(即,在研究完成和揭盲之后)的靶标接合。健康志愿者中PBMC的易于获取有利于测量健康志愿者外周血中的MGLL靶标接合。

[0132] 在一些实施方案中,还分析了来自受试者的血液样品中不同于2-AG或除2-AG之外的一种或多种内源性脂质。在进一步的实施方案中,该一种或多种内源性脂质包括但不限于花生四烯酸乙醇胺和其他单酰甘油物质。在一些实施方案中,该一种或多种内源性脂质为花生四烯酸乙醇胺。

[0133] 药物组合物

[0134] 本文公开了用于治疗炎症或神经性疼痛的药物组合物,其中每种药物组合物均包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

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的盐的有效剂量为约1mg至约450mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约400mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约350mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约150mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约25mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约15mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约400mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约350mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约150mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约25mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约160mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约75mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约25mg。

[0144] 本文公开了用于治疗炎症或神经性疼痛的药物组合物,其中每种药物组合物均基本由有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂组成,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约

2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0145] 本文公开了用于治疗神经性疼痛的药物组合物,其中每种药物组合物均基本由有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂组成,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0146] 本文公开了用于治疗炎症的药物组合物,其中每种药物组合物均基本由有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂组成,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0147] 本文公开了用于治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的药物组合物,其中每种药物组合物均包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0148] 本文公开了用于治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的药物组合物,其中每种药物组合物均包含有效剂量的化合物1或其药学上可接受的盐以及一种或多种药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0149] 本文进一步公开了用于治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg、约2mg、约3mg、约4mg、约5mg、约6mg、约7mg、约8mg、约9mg、约10mg、约11mg、约12mg、约13mg、约14mg、约15mg、约16mg、约17mg、约18mg、约19mg、约20mg、约21mg、约22mg、约23mg、约24mg、约25mg、约26mg、约27mg、约28mg、约29mg、约30mg、约31mg、约32mg、约33mg、约34mg、约35mg、约36mg、约37mg、约38mg、约39mg、约40mg、约41mg、约42mg、约43mg、约44mg、约45mg、约46mg、约47mg、约48mg、约49mg、约50mg、约55mg、约60mg、约65mg、约70mg、约75mg、约80mg、约85mg、约90mg、约95mg、约100mg、约110mg、约120mg、约130mg、约140mg、约150mg、约160mg、约170mg、约180mg、约190mg、约200mg、约210mg、约220mg、约230mg、约240mg、约250mg、约260mg、约270mg、约280mg、约290mg、约300mg、约310mg、约320mg、约

330mg、约340mg、约350mg、约360mg、约370mg、约380mg、约390mg、约400mg、约410mg、约420mg、约430mg、约440mg、约450mg、约460mg、约470mg、约480mg、约490mg或约500mg,包括其中的增量。

[0150] 本文进一步公开了用于治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎 (NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约450mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约400mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约350mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约150mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约25mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约15mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约400mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约350mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约150mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约25mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约160mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约75mg。在一些实施方案中,在本文公

开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约25mg。

[0151] 本文公开了用于治疗癫痫/癫痫发作、多发性硬化、视神经脊髓炎(NMO)、图雷特综合征、阿尔茨海默病或与肠易激综合征相关的腹痛的药物组合物,其中每种药物组合物均基本由有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂组成,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0152] 本文公开了用于治疗急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的药物组合物,其中每种药物组合物均包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

[0153] 本文公开了用于治疗急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的药物组合物,其中每种药物组合物均包含有效剂量的化合物1或其药学上可接受的盐以及一种或多种药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,所述有效剂量为约2mg至约400mg。在一些实施方案中,所述有效剂量为约10mg至约160mg。在一些实施方案中,所述有效剂量为约2mg至约100mg。在一些实施方案中,所述有效剂量为约2mg至约50mg。在一些实施方案中,所述有效剂量为约2mg至约20mg。

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400mg、约410mg、约420mg、约430mg、约440mg、约450mg、约460mg、约470mg、约480mg、约490mg或约500mg,包括其中的增量。

[0155] 本文进一步公开了用于治疗急性疼痛、炎性疼痛、癌症疼痛、由周围神经病变引起的疼痛、中枢性疼痛、纤维肌痛、偏头痛、镰状细胞病血管阻塞性疼痛危象、与多发性硬化相关的痉挛或疼痛、功能性胸痛、类风湿性关节炎、骨关节炎或功能性消化不良的药物组合物,其中所述药物组合物包含有效剂量的化合物1或其药学上可接受的盐以及药学上可接受的赋形剂,其中所述有效剂量为约1mg至约500mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约450mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约400mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约350mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约150mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约25mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约1mg至约15mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约400mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约350mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约150mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约2mg至约25mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约300mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约250mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约200mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约160mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约100mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至

约75mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约50mg。在一些实施方案中,在本文公开的方法中施用的化合物1或其药学上可接受的盐的有效剂量为约10mg至约25mg。

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[0157] 以下实施例仅作为多个实施方案的说明提供,而不应被解释为以任何方式限制本发明。

实施例

实施例1. 体外药理学

[0158] 化合物1是人、小鼠、大鼠和狗MGLL的有效抑制剂,且其在上述所有物种中的 $IC_{50} < 30nM$ 。采用基于活性的蛋白质谱分析(ABPP)来测定体外效力,该基于活性的蛋白质谱分析是使用化学探针以活性依赖性方式共价修饰酶活性位点的功能性蛋白组学技术(例如,仅催化活性的酶将与ABPP探针反应并被标记有ABPP探针)。采用聚丙烯酰胺凝胶电泳或质谱法来实现被探针标记的蛋白质的鉴别。用化合物1来体外处理组织或细胞匀浆,随后将其与探针一起温育、进行凝胶电泳和荧光成像,从而允许进行化合物1的靶标的直接可视化和定量。

[0159] 化合物1对小鼠、大鼠、狗和人脑组织以及由2个人细胞系(PC3前列腺癌细胞和表达重组hMGLL的人胚肾[HEK]293T细胞)制备的裂解物中的MGLL的抑制效力以预温育30分钟后的 IC_{50} 计算。表1中总结了 IC_{50} 值。MGLL通过凝胶电泳作为大约34kDa的多种分子量种类迁移。化合物1显示出对所有MGLL同种型的等效抑制效力。

[0160] 表1. 通过ABPP测定的化合物1对小鼠、大鼠、狗以及人组织和细胞匀浆中的MGLL的体外效力

物种	来源	MGLL IC ₅₀ (μ M)
小鼠	脑*	0.027 $\pm$ 0.003
大鼠	前额皮质 [†]	0.026 $\pm$ 0.006
狗	前额皮质 [†]	0.012 $\pm$ 0.002
人	PC3 细胞 [†]	0.014 $\pm$ 0.005
	前额皮质 [†]	0.021 $\pm$ 0.004
	重组体 [‡]	0.008 $\pm$ 0.005

缩写: ABPP=基于活性的蛋白质谱分析,即一种采用与在机制上相关的酶类别反应的化学探针的功能性蛋白组学技术; IC₅₀=产生50%抑制的浓度; MGLL=单酰基甘油脂肪酶。

其他信息: 在ABPP分析前将化合物1 (0–10 μ M) 与所列出的来源物质在37℃下预温育30min。数据表示来自若干次独立实验的平均值 $\pm$ 平均值标准误差 (SEM): *n=10, [†]n=3, [‡]n=2。

[0161] 还采用基于质谱法 (MS) 的2-AG底物测定来评估人脑组织中化合物1的活性。在从人脑皮质样品制备的匀浆中, 化合物1抑制94%的2-AG向AA的转化, 且IC₅₀为1.7nM。通过基于凝胶的ABPP评价了完整人PC3前列腺癌细胞中的细胞效力, 其中化合物1以2.2nM的IC₅₀抑制MGLL活性。

实施例2. 体内药理学

[0162] A. MGLL靶标接合、2-AG浓度和化合物1浓度之间的关系

[0163] 蛋白质活性位点被小分子的占据和抑制被称为靶标接合 (即, 药物如何稳健地与靶标相互作用的近端标志物)。在非人灵长类动物中使用PET, 并且在啮齿类动物和狗中使用ABPP来测量MGLL被化合物1的靶标接合。MGLL靶标接合抑制了2-AG的水解, 从而提高了组织2-AG浓度, 该组织2-AG浓度可通过MS在啮齿类动物的组织和体液中测量。2-AG的提高导致大麻素受体信号传导和生理学响应增强。这些研究的目标在于测量在动物中施用化合物1后的MGLL靶标接合、2-AG浓度和化合物1浓度。

[0164] 使用标记形式的MGLL抑制剂评价了恒河猴脑部的MGLL靶标接合。在恒河猴中, 该标记的MGLL抑制剂表现出脑部渗透性和与含CB₁的神经元中的MGLL的已知表达相一致的区域分布。采用将基线处和化合物1施用后的标记的MGLL抑制剂结合进行比较的封闭方案评价了恒河猴脑部MGLL被化合物1的占据。化合物1的单剂量IV施用 (0.01–1mg/kg, PET示踪物之前90min, 2只动物) 以0.047 $\pm$ 0.025mg/kg的ED₅₀参与恒河猴脑部的MGLL (参见图1)。

[0165] 采用0.2的分数吸收因子 (20%生物利用度) 从单剂量静脉内施用计算了针对靶标接合 (而非功效) 的口服等同ED₅₀剂量。

[0166] 来自经化合物1治疗的啮齿类动物的组织和细胞的ABPP分析允许MGLL抑制的体内直接可视化和定量。向大鼠单剂量口服灌胃 (PO) 施用化合物1 (高达30mg/kg, 4小时, n=3–10, 4次独立实验) 以0.6mg/kg的平均ED₅₀抑制脑部的MGLL活性。在大鼠肝脏 (0.1mg/kg的

ED₅₀)、心脏(0.08mg/kg的ED₅₀)和PBMC(0.1mg/kg的ED₅₀)中还观察到MGLL活性的剂量依赖性抑制。

[0167] MGLL抑制导致2-AG在啮齿类动物脑部和外周中的积累。在单次口服剂量的化合物1(高达30mg/kg,4小时,n=3-10,3次独立的实验)后,大鼠前脑2-AG浓度相对于对照水平提高≥10倍,并且与脑部MGLL活性呈负相关。脑部2-AG浓度提高,且平均ED₅₀值为1.3mg/kg。2-AG积累(ED₅₀为1.3mg/kg)相对于MGLL抑制(ED₅₀值为0.6mg/kg)降低的效力反映了这样的观察,即在观察到2-AG积累之前需要将MGLL活性抑制大约50%。内源性大麻素花生四烯酸乙醇胺的大鼠脑部水平未被化合物1提高,表明这些浓度下的化合物1并不抑制主要的花生四烯酸乙醇胺水解酶FAAH。在单次口服剂量的化合物1后,大鼠血浆和肝脏中2-AG的浓度分别提高7倍和大约3至5倍。脑部、肝脏和血液的化合物1浓度随着化合物1剂量的增加而增加,并且与MGLL抑制和2-AG浓度呈正相关。

[0168] 化合物1对小鼠中的MGLL活性、2-AG浓度和化合物1浓度产生类似的剂量依赖性作用。化合物1的单剂量PO施用(2-32mg/kg,4小时,n=3)分别以1.4mg/kg和0.5mg/kg的ED₅₀值抑制小鼠脑部和肝脏中的MGLL活性。在化合物1治疗后,小鼠脑部2-AG浓度增加高达30倍。

[0169] 采用固定指数异速生长,基于大鼠和猴子ED₅₀数据的预计的人口口服ED₅₀等同剂量在4.4至8.6mg范围内。

[0170] B. 化合物1浓度、MGLL抑制和2-AG浓度的时程以及MGLL活性的恢复

[0171] 在大鼠中评价了单剂量化合物1(0.5-10mg/kg,给药后最多144小时,n=3,3次独立实验)的时程效应。在大鼠脑部,化合物1显示出对MGLL活性的时间依赖性效应。化合物1的化合物浓度与MGLL活性的抑制和2-AG的水平呈正相关(参见图2A-C)。在给药后的4小时观察到接近最大的MGLL抑制和2-AG积累,这支持将4-小时时间点用于行为研究。

[0172] 在化合物1从大鼠脑部清除后(即,到达低于定量极限的水平[BLQ]),MGLL活性以每小时大约2%的平均速率恢复(参见图2D)。大鼠脑部的MGLL活性的恢复速率与在其他大鼠组织和培养的人细胞中共价MGLL抑制后所观察到的相似。一旦大鼠脑部的MGLL活性恢复至治疗前活性的大约50%,则脑部2-AG浓度回到基础水平(参见图2B)。

[0173] 在小鼠中的单剂量化合物1后观察到对脑部MGLL活性、2-AG浓度和化合物1浓度的类似的时间依赖性效应。

[0174] C. 啮齿类动物疼痛模型中的功效

[0175] 使用大鼠福尔马林爪测试作为主要的临床前模型来评估化合物1的PK/PD关系并且提供人剂量预测。福尔马林爪测试是通过将福尔马林局部注射至后爪而诱导的疼痛模型,该疼痛模型产生由直接刺激伤害感受器引起的早期反应和由炎症和中枢致敏引起的延迟反应。在用化合物1进行的研究中,通过使用自动化系统对舔爪的持续时间和频率进行评分来追踪痛觉。

[0176] 化合物1的单剂量施用(高达10mg/kg,PO,测试前4小时,n=10,2次独立实验)在福尔马林-攻击的大鼠中引起剂量依赖性的抗疼痛作用,并减少了早期(第1期)和延迟期(第2期)中的舔爪行为(参见图3B)。将0.5mg/kg的第2期ED₅₀用于评估PK/PD关系。采用单剂量的 α -2, δ -1钙通道阻滞剂普瑞巴林(30mg/kg,PO,n=10)观察到类似的抗疼痛反应,普瑞巴林是一种用于治疗神经性疼痛的临床有效的止痛剂。大鼠福尔马林模型中化合物1的PK/PD关系,以及脑部MGLL活性和2-AG浓度在图3A-D中示出。这种关系表明,化合物1在部分抑制

脑部MGLL并引起脑部2-AG浓度的次最大提高的剂量下在大鼠福尔马林测试中实现了功效。大鼠福尔马林测试的第2期中0.5mg/kg的ED₅₀对应于5nM的脑部化合物1浓度、7nM的血液化合物1浓度、脑部MGLL活性的大约40%抑制,以及脑部2-AG浓度大约3倍的提高。

[0177] 在单个研究中探讨了大鼠福尔马林模型中化合物1的多剂量施用(0.5-10mg/kg, 5天QD, n=10)的效果。尽管以部分抑制MGLL(1mg/kg)的剂量单次和重复施用化合物1使疼痛行为在数值上减少相同的程度,但重复剂量组中的效果与媒介物无统计学差异。

[0178] 与在大鼠福尔马林防伤害模型中的功效相关的化合物1暴露的ED₅₀为0.4μM·hr。功效(防伤害舔爪行为)和靶标接合(通过基于离体活性的蛋白质谱分析)的单次口服ED₅₀剂量具有相似的量级。防伤害功效的D₅₀剂量也是最低有效剂量。在大鼠的ED₅₀剂量和高20倍的口服剂量(在福尔马林攻击模型中评价的化合物1的最高剂量)下,除了所观察到的抗防伤害行为之外的显性的行为或运动扰动并不明显。仅当MGLL活性被抑制大于约40-50%时,大鼠脑部2-AG浓度才变得可测量地升高。

实施例3. 采用化合物1的大鼠PBMC中的MGLL抑制和血浆2-AG水平的测定

[0179] 向大鼠施用单次PO剂量的化合物1(高达30mg/kg, 4h, n=2-3)。大鼠PBMC中的MGLL活性以剂量依赖性方式降低,且中值有效剂量(ED₅₀)为0.07mg/kg并且血浆2-AG水平增加高达7倍(参见图4A-B)。通过ABPP分析来评估PBMC裂解物中的MGLL活性,并通过液相色谱串联质谱法(LC-MS/MS)测量血浆2-AG浓度。

实施例4. 采用化合物1的人PBMC中的MGLL抑制的测定

[0180] 可通过ABPP分析(参见图4A)或通过测量AA产物形成的基于质谱的2-AG底物测定(参见图5B)容易地评估人PBMC中的MGLL活性。化合物1(0.0003-1000nM, 30min, 37℃)在获自两个健康人供体的人全血中的温育以47nM的IC₅₀抑制所分离的PBMC中的MGLL活性(参见图5B)。

实施例5. 胶囊制剂

[0181] 将化合物1的盐酸盐配制成含有2.14、10.72和53.60mg盐酸盐(分别相当于2、10和50mg化合物1)(盐因子=1.07)的填充粉末的明胶胶囊。所使用的明胶胶囊壳为2号,并且盖和主体的颜色均为瑞典橙。

[0182] 胶囊制剂中使用的赋形剂为:微晶纤维素、交联羧甲基纤维素钠、硬脂酸镁(来源于植物)和明胶胶囊壳。胶囊壳由明胶、红色氧化铁和二氧化钛组成。所有赋形剂都符合EP/USP/NF的规格。

[0183] 匹配的安慰剂胶囊(化合物1盐酸盐胶囊的安慰剂)含有相同的赋形剂。在安慰剂制剂中,用微晶纤维素替代化合物1的盐酸盐。

[0184] 稳定性研究表明,这样的化合物1盐酸盐胶囊在40℃/75%相对湿度的加速贮存条件下稳定长达2个月。进一步的稳定性研究表明,这样的化合物1盐酸盐胶囊在40℃/75%相对湿度的加速贮存条件下稳定长达6个月。在长期的加速的贮存条件下在散装容器(30ct/45cc瓶)中的稳定性研究与I期试验同时进行。

[0185] 在长期的加速的贮存条件下匹配安慰剂胶囊的稳定性研究也与I期试验同时进行。

实施例6. 用于评价化合物1盐酸盐的安全性、耐受性、药代动力学和药效学的单剂量和多剂量研究。

[0186] 总体设计和方法：本研究的目的在于评估化合物1（作为化合物1盐酸盐的胶囊施用）在健康成年人中的初始安全性、耐受性、药代动力学和药效学。在该研究的第1部分中，在最多4个治疗时段内向个体受试者施用单次口服剂量的化合物1的盐酸盐（或匹配的安慰剂）。在该研究的第2部分中，向个体受试者每日施用口服剂量的化合物1的盐酸盐（或匹配的安慰剂），持续最长14天。使用来自本研究的数据来选择后续临床研究的剂量和给药方案。

[0187] 这是一项随机化双盲带安慰剂对照的研究，用于探讨化合物1盐酸盐的递增单次口服剂量（第1部分，A组和B组）和递增多次每日口服剂量（第2部分，C-G组）在健康成年受试者中的安全性、耐受性、药代动力学（PK）和药效学（PD）。

[0188] 在第1部分中，A组和B组均由在以交替的方式进行的最多4个治疗时段（治疗时段1至4）中的八名健康男性成年受试者（随机化成以3:1的比例分别接受单次递增剂量的化合物1盐酸盐或匹配的安慰剂）组成。在A组中评估了高脂肪早餐对化合物1盐酸盐的药代动力学的影响。

[0189] 在第2部分中，C组至G组均由八名健康成年受试者（随机化成以3:1的比例分别接受化合物1盐酸盐或匹配的安慰剂）组成，每日一次，持续最长14天。在第2部分中，依次向各组给药。

[0190] 由于这是化合物1盐酸盐在人中的1期评估，并且鉴于该化合物的药代动力学、药效学 and 安全性特征仍有待评价，因此该方案被编写得具有一定的灵活性以适应1期临床试验的固有动态性质。

[0191] 目标：

[0192] 第I部分，主要目标：评价在向健康男性成年受试者施用单次递增口服剂量的化合物1盐酸盐后，化合物1的安全性和耐受性。

[0193] 第1部分，次要目标：(1) 获得在向健康男性成年受试者施用单次递增口服剂量后，化合物1的盐酸盐的初步血浆药代动力学（例如， C_{max} 、 T_{max} 、 AUC_{0-t} 、 AUC_{0-inf} 、 $t_{1/2}$ ）。假设：在一个或多个良好耐受的单次口服剂量的化合物1盐酸盐下，化合物1的几何平均 AUC_{0-inf} 为至少 $0.4\mu M \cdot hr$ 。(2) 将在向健康男性成年受试者施用单次递增口服剂量之后高脂肪早餐对化合物1盐酸盐的血浆药代动力学的影响与处于禁食状态的那些受试者进行比较。估计：估计了在向健康男性成年受试者口服施用单剂量的化合物1的盐酸盐之后，标准化高脂肪早餐对化合物1盐酸盐的血浆药代动力学（例如， C_{max} 、 T_{max} 、 AUC_{0-inf} ）的影响。(3) 获得在向健康男性成年受试者施用单次递增口服剂量的化合物1的盐酸盐后，关于完整药物的尿排泄的初步数据。

[0194] 第2部分，主要目标：评价化合物1的盐酸盐作为多个每日口服剂量向健康成年受试者施用最长连续14天的安全性和耐受性。

[0195] 第2部分，次要目标：(i) 评估在向健康成年受试者施用多个每日口服剂量的化合物1盐酸盐持续最长连续14天后，化合物1盐酸盐的单剂量的稳态时间-血浆浓度曲线和药代动力学参数值（例如， C_{max} 、 T_{max} 、 AUC_{0-24h} 、 AUC_{0-tau} 、 $t_{1/2}$ 、积累率）。假设：在一个或多个良好耐受的每日口服剂量的化合物1盐酸盐下，化合物1的稳态几何平均 AUC_{0-24h} 为至少 $0.4\mu M \cdot hr$ 。(2) (如果进行了测量) 获得在向健康成年受试者施用多个每日口服剂量的化合物1的盐酸盐后，关于完整药物的尿排泄的初步数据。

[0196] 受试者数目(预计):

[0197] 第1部分:十六名年龄在18岁至55岁之间的健康成年男性受试者参加该研究的第1部分。八名不同的受试者(随机化成接受化合物1的盐酸盐或匹配的安慰剂)参与该研究的每一组(A组和B组)。

[0198] 第2部分:多达四十名年龄在18岁至55岁之间的健康成年受试者(男性或无生育能力的女性)参加该研究的第2部分。八名不同的受试者(随机化成接受化合物1的盐酸盐或匹配的安慰剂)参与该研究的每一组(C组至G组)。

[0199] 入选标准:

[0200] A) 受试者理解研究过程并且通过提供书面知情同意书同意参与该研究。

[0201] B) 第1部分:受试者为男性,研究前/筛选访视时的年龄为18岁至55岁。

[0202] C) 第2部分:受试者为男性或女性(不具有生育能力),研究前/筛选访视时的年龄为18岁至55岁;另外:

(1) 如果受试者为绝经后的女性:受试者至少1年没有月经,并且有记录表明在试验前(筛选)促卵泡激素(FSH)水平在绝经后的范围内。

(2) 如果受试者为手术绝育的女性:受试者处于子宫切除术、双侧卵巢切除术或输卵管结扎术后的状态。(如果没有记录证明,则可通过超声或其他成像技术来确认子宫切除术。卵巢切除术和输卵管结扎必须由记录证实)。

[0203] D) 受试者在研究前/筛选访视时具有 >18 至 $\leq 30\text{kg/m}^2$ 的身体质量指数(BMI)。BMI = 体重(kg) / 身高(m)² (BMI计算应四舍五入成最接近的整数)。

[0204] E) 基于病史、身体检查和生命体征测量以及在研究前/筛选时和首次施用研究药物前24小时内获得的实验室安全性测试,受试者被判断为处于良好健康状态。

[0205] F) 受试者在研究前/筛选时以及首次施用研究药物之前的心电图(ECG)没有临床上显著的异常。

[0206] G) 受试者不抽烟并且/或者在至少约3个月内未曾使用尼古丁或含尼古丁的产品(例如,尼古丁贴剂)。

[0207] H) 受试者愿意遵守研究限制条件。

[0208] I) 第1部分:受试者愿意食用方案指定的高脂肪早餐。

[0209] 排除标准:

[0210] A) 受试者的年龄低于法律许可的年龄。

[0211] B) 受试者具有临床上有意义的精神病学疾病(包括严重情感障碍、精神病倾向和药物引起的精神病)的个人病史。过去曾患有境遇性抑郁或焦虑的受试者可由研究者决定是否可参加。

[0212] C) 受试者有精神分裂症、重大情感障碍或其他精神病的一级家族史。

[0213] D) 受试者在精神上或法律上是无行为能力的,在研究前/筛选访视时有明显的情绪问题,或预计在研究进行中会有精神失常的可能。

[0214] E) 受试者具有在研究调查者看来可能混淆研究结果或可能由于参与研究而给受试者造成额外风险的任何疾病史。

[0215] F) 根据Cockcroft-Gault方程,受试者的肌酐清除率(CrCl)估计值 $\leq 80\text{mL/min}$ 。如使用24小时尿液收集测量的实际肌酐清除率可替代Cockcroft-Gault计算或与Cockcroft-

Gault计算结合使用。实际或计算的肌酐清除率在72-79mL/min范围内(即,在80mL/min的10%以内)的受试者可由研究者决定是否可参加。

Cockcroft-Gault方程:

$$\text{CrCl} = (140 - \text{年龄}[\text{岁}]) * (\text{体重}[\text{kg}]) / (72) \text{ 血清肌酐}[\text{mg/dL}]$$

注意:对于女性受试者,将该值乘以0.85来获得肌酐清除率。

[0216] G) 受试者具有中风、慢性癫痫或重大神经紊乱史。

[0217] H) 受试者具有临床上有意义的内分泌、胃肠道、心血管、外周血管、血液、肝、免疫、肾、呼吸系统或泌尿生殖系统异常或疾病史。具有不复杂的肾结石(定义为自发通过,且过去5年内无复发)或儿童哮喘史的受试者可由研究者决定是否可参加试验。

[0218] I) 受试者有临床上有意义的肿瘤疾病史,经充分治疗的皮肤(即,基底细胞癌)或宫颈的局部或原位非黑素瘤癌除外。

[0219] J) 受试者有显著的多重变态反应和/或严重变态反应(例如,食物、药物、乳胶变态反应)史,或者曾对方药或非处方药(包括大麻或其他含有大麻的药物)或食物有过敏反应或显著不耐受性。

[0220] K) 受试者曾进行大手术、曾捐献或失去1个单位(大约500mL)的血液,或在研究前/筛选访视前4周内参与了另一项研究性试验。该4周窗口来源于从先前试验的最后试验药物和/或血液收集和/或与试验药物相关的不良事件(AE)到当前试验的试验前/筛选访视的日期。对于曾参与未施用试验药物或未进行侵入性程序的研究性试验的受试者,该间隔可被修改成不包括间隔要求。

[0221] L) 受试者(在研究前/筛选访视的8周内)曾进行预防性疫苗接种或计划在研究过程期间(即,直至研究后访视)进行预防性疫苗接种。

[0222] M) 从施用研究药物的初始剂量之前大约2周(或5个半衰期)开始,经过整个研究(包括治疗时段之间的清除间隔),直到研究后访视,受试者无法避免或预期会使用任何药物,包括处方药和非处方药或草药(如St. John's Wort[贯叶金丝桃(Hypericum perforatum)])。可能有某些药物是允许的。

[0223] N) 受试者饮用大量酒精,定义为每天>3份酒精饮料(1份大约相当于:300mL[10盎司]啤酒,125mL[4盎司]葡萄酒,25mL[1盎司]蒸馏酒)。每天饮用不超过4份酒精饮料的受试者可由研究者决定是否可参加。

[0224] O) 受试者消耗大量的咖啡因,定义为每天>6份咖啡、茶、可乐或其他含咖啡因的饮料(1份大约相当于120mg咖啡因)。

[0225] P) 受试者目前(定义为在研究前/筛选访视的大约3个月内)是任何非法药物(包括大麻)的常规使用者(包括“娱乐性使用”),或在研究前/筛选访视的大约6个月内有药物(包括酒精)滥用史。

[0226] Q) 对于男性受试者:受试者不愿意或者不能够在研究药物的第一次施用直到研究药物的最后剂量后三个月的时间内与女性性伴侣使用避孕套。

[0227] R) 对于男性受试者:受试者不愿意在研究药物的第一次施用直到研究药物的最后剂量后三个月的时间内避免精子捐献。

[0228] S) 受试者有长QT综合征家族史。

[0229] T) 受试者的QTc间隔>450msec(基于在基线处获得的一式三份ECG的平均值)。

[0230] U) 研究者担心研究中受试者的安全参与,或出于任何其他原因,研究者认为受试者不适于参与该研究。

[0231] 研究产品、剂量和施用模式:研究药物产品——化合物1盐酸盐的胶囊和匹配的安慰剂作为配制用于口服施用的2mg、10mg和50mg (游离碱当量) 干燥粉末的胶囊提供给临床研究单位。研究药物以适当标记的散装包装提供至临床点。在其他方面与研究的进行无关的临床点的非不知情药剂师(或在非不知情药剂师的直接监督下的指定人员) 根据所提供的分配计划表将用于施用的盲法研究药物分发给受试者。对于第2部分,用于支持各个受试者的给药持续长达整个给药持续时间(即,14天)的研究药物可在临床点由非不知情药剂师(或在非不知情药剂师的直接监督下的指定人员) 重新包装。这些重新包装的盲法临床供给品仅施用给临床点的受试者。

[0232] 治疗持续时间:

[0233] 第1部分:对于第1部分,总的研究参与为大约84天(包括28天的筛选期)。在第1部分中的治疗之间存在至少7天的最短清除期。

[0234] 第2部分:对于第2部分,总的研究参与为大约56天(包括28天的筛选期)。

[0235] 参考疗法、剂量和施用模式:

[0236] 第1部分:在A组和B组中,每名受试者均在最多4个治疗时段中接受单次递增口服剂量的化合物1盐酸盐或匹配的安慰剂,该4个治疗时段被剂量之间的最短1周清除间隔所隔开。在A组和B组中,研究药物的施用之间存在最短72小时的时段。此外,在B组第2时段与A组第3时段之间存在最短2周的清除,以便在进行第3和第4时段的给药之前评价可用的初步药代动力学数据以及来自先前剂量的安全性和耐受性数据。所有剂量都与大约240mL的水一起口服施用。在研究药物施用之前的1小时和施用之后的1小时限制饮水。在除了A组第4时段(食物影响治疗时段)之外的每个治疗时段中,研究药物均在整夜禁食(持续大约8小时)后施用。

[0237] A组:受试者在第1至4时段中接受单次2mg、18mg、100mg和18mg (伴随食物) 剂量的化合物1盐酸盐(n=6) 或匹配的安慰剂(n=2)。第2和4时段(禁食与进食)的分配计划表相同,使得相同受试者在各自的治疗时段中接受活性药物或匹配的安慰剂。

[0238] 在A组第4时段中,研究药物在进食高脂肪早餐后施用。该高脂肪早餐的组成为:2片煎蛋或炒鸡蛋,2条培根,带有2块黄油的2片烤面包,4盎司(113克)炸土豆饼(煎土豆),240mL全脂牛奶(营养成分约55.6克脂肪,55克碳水化合物,31.1克蛋白质;总卡路里=500.4脂肪,220碳水化合物,124.4蛋白质)。在该食物影响治疗时段中,受试者在研究药物施用前大约8小时内还禁食所有食物和除水之外的饮品。然而,在研究药物施用前大约30分钟,受试者开始进食如上所述的高脂肪早餐。这餐应在20分钟的时间内全部食用。在食用该餐后大约10分钟,向受试者施用其剂量的研究药物和大约240mL水,并且在研究药物施用后再另外限制水1小时。

[0239] B组:受试者在第1至4时段中接受单次6mg、50mg、200mg和400mg剂量的化合物1盐酸盐(n=6) 或匹配的安慰剂(n=2)。

[0240] 表2中提供了针对第1部分(A组和B组)中的剂量递增的化合物1的盐酸盐的建议剂量。

表2.

组: a),b),c)	第 1 时段	第 2 时段	第 3 时段	第 4 时段
A 组	2 mg	18 mg ^{d)}	100 mg	18 mg (进食) ^{e)}
B 组	6 mg	50 mg	200 mg	400 mg

^{a)} 受试者被随机化成接受单次口服剂量的化合物1盐酸盐 (n=6) 或匹配的安慰剂 (n=2)。

^{b)} 不同的受试者参与每个组。

^{c)} 可基于对先前组或治疗时段的安全性、耐受性和/或药代动力学数据的评价,向下调整所述剂量。

^{d)} 对于A组受试者,第4时段中指定的治疗与第2时段中的治疗相同,使得相同的受试者在这两个治疗时段中接受安慰剂。

^{e)} 待与高脂肪早餐一起施用的化合物1的盐酸盐;基于第2时段中接受的剂量针对每个受试者重复化合物1的盐酸盐的剂量。

[0241] 应注意,这里建议的剂量可基于先前组或时段的初步药代动力学、安全性和耐受性数据而向下调整。

[0242] 在该研究中的受试者的初步药代动力学数据指导剂量递增至更高的剂量。在B组第2时段后出现药代动力学停顿,以便在A组第3时段中进一步剂量递增之前评估可用的药代动力学数据以及安全性和耐受性数据。所计划的剂量可基于对先前组或治疗时段的安全性、耐受性和/或药代动力学数据的评价而向下调整。

[0243] 第2部分:在C组至G组中,每个受试者均接受每日口服剂量的化合物1的盐酸盐或匹配的安慰剂,持续最长14天。所有剂量都与大约240mL的水一起口服施用。在研究药物施用之前1小时和施用之后1小时限制饮水。仅在初步药代动力学、安全性和耐受性数据可从第1部分A组第3时段(100mg剂量)获得的情况下开始第2部分。在第2部分第一组(即,C组)中的给药前,向研究者和伦理审查委员会(ERC)/机构审查委员会(IRB)提供剂量选择备忘录/临时报告。在研究者从ERC/IRB接收到针对C组选定的剂量的批准之前,不进行C组中的给药。各组按顺序进行:仅在先前组的给药期的安全性和耐受性数据的初步评价已经进行之后才开始后续组的给药(D、E、F和G组的第一次给药分别与C、D、E和F组的最终给药之间不少于一周)。在每个治疗时段中,研究药物均在整夜禁食后(持续大约8小时)施用。

[0244] C组:受试者接受每日口服10mg剂量的化合物1的盐酸盐 (n=6) 或匹配的安慰剂 (n=2),持续最长14天。

[0245] D组:受试者接受每日口服20mg剂量的化合物1的盐酸盐 (n=6) 或匹配的安慰剂 (n=2),持续最长14天。

[0246] E组:受试者接受每日口服40mg剂量的化合物1的盐酸盐 (n=6) 或匹配的安慰剂 (n=2),持续最长14天。

[0247] F组:受试者接受每日口服80mg剂量的化合物1的盐酸盐 (n=6) 或匹配的安慰剂 (n=2),持续最长14天。

[0248] G组:受试者接受每日口服160mg剂量的化合物1的盐酸盐 (n=6) 或匹配的安慰剂

(n=2), 持续最长14天。

[0249] 应注意, 这里建议的剂量可基于先前组或治疗时段的初步药代动力学、安全性和耐受性数据而向下调整。

[0250] 对于所有单次剂量(即, 第1部分的所有剂量)和第2部分中施用的第一剂量(第1天)和最后剂量(第14天), 所有受试者均在给药后最少约4小时内禁食(除了水之外, 在给药后1小时开始允许进水)。在给药后大约4小时施用标准化午餐, 在给药后大约10小时施用标准化晚餐, 并且可在给药后7小时和13小时提供零食。对于本研究的目的, “标准化”是指在整个治疗时段和组中, 卡路里含量和组成应该是相似的。对于非给药日(第1部分)以及对于非给药日和第2天直到第13天的给药日(第2部分), 饮食不必是标准化的。

[0251] 表3中提供了针对第2部分(C组至G组)中的剂量递增的化合物1的盐酸盐的建议剂量。

表3.

a), i), ii) 组:	C 组	D 组	E 组	F 组	G 组
化合物 1 盐酸盐的剂量	10 mg	20 mg	40 mg	80 mg	160 mg

a) 受试者被随机化成接受单次口服剂量的化合物1盐酸盐 (n=6) 或匹配的安慰剂 (n=2)。

i) 不同的受试者参与每个组。

ii) 可基于对先前组或治疗时段的安全性、耐受性和/或药代动力学数据的评价, 向下调整所述剂量。

[0252] 评价标准:

[0253] 药代动力学/药效学:

- 用于确定化合物1血浆和尿液浓度的血液和尿液。

[0254] 可分析尿液用于定性代谢物表征。

[0255] 在第1部分中, 视情况在给药前以及在第1部分的选定治疗时段中给药后的最长48小时收集用于确定尿液化合物1浓度的尿液样品(在最高预期剂量(SAD)下, 并且仅在一个治疗时段内)。

[0256] 在每个治疗组的第14天的研究药物最后剂量后的最长48小时内收集尿液样品(以两个收集等分试样的形式: 0-24h和24-48h)。基于第1部分的初步尿液PK数据来作出测定这些尿液样品的决定, 以进行化合物1定量和尿排泄表征以及可能的定性代谢物表征。基于这些第1部分尿液PK数据, 没有测定或测定了第2部分中收集的尿液PK样品中的一些或全部。此外, 基于初步数据, 后续组中的尿液收集可以间断。如有必要并且为了提高检测的灵敏度, 可在分析前将来自给定组的受试者的尿液样品合并。

[0257] 安全性: 通过不良事件的临床评估, 通过生命体征、身体检查、体重、神经学检查、12导联心电图(ECG)的重复测量以及通过标准临床实验室安全性测试(血液学、化学和尿分析)来监测化合物1的盐酸盐的安全性和耐受性。

[0258] 不良事件询问在0小时(给药前)和整个研究的每次访视, 直至并包括研究后访视

(研究药物的最后剂量后至少14天)时进行。

[0259] 统计学方法:

[0260] 样本大小/功效:用于初始人体安全性研究的样本大小是受限的,并基于习惯值进行选择。由于甚至几乎不知道实际的比例,因此用于比较不良事件率的功效计算太不精确,而不具有临床意义。然而,如果不良事件以1%或10%的比例发生,则在接受该剂量的6名受试者中观察到这样的不良事件的概率分别为6%或47%。如果在给定剂量下的6名受试者中的任一名中均未观察到给定类型的AE,则在80% (90%) 置信度下在该剂量下不良事件的真实发生率为至多24% (32%)。

[0261] 随机化:根据计算机生成的随机码将受试者在队列内随机化。

[0262] 统计学方法:

[0263] PK:描述性统计学由治疗(第1部分)以及由治疗和日期(第2部分)提供。提供了所有PK参数的最小值、中值、最大值和CV。提供了AUC和C_{max}的基于原始尺度的算术平均值和标准偏差。此外,还根据下式提供并计算了AUC和C_{max}的百分比CV: $100 \times \sqrt{\exp(s^2) - 1}$, 其中s²为在自然对数尺度上观察到的变化。提供了半衰期的谐波平均和折刀式(jack-knife)SD。以探索性的方式评价了达到稳态的时间和PK线性度。

[0264] 药效学:

[0265] 第1部分

[0266] 使用描述性统计学通过时间点和治疗列出并总结了单剂量2-AG浓度和MGLL TE百分比。计算了每个受试者和每个基线后时间点的基线百分比。基线被定义为每个时段的测试治疗之前的最后样品中的水平。经由对数尺度汇总统计的逆转换来计算基线百分比。可类似地总结其他PD读数。

[0267] 第2部分

[0268] 使用描述性统计学通过日期和治疗列出并总结了多剂量2-AG浓度和MGLL TE百分比。对于每个受试者和每个基线后时间点,经由对数尺度汇总统计的逆转换来计算基线百分比。可类似地总结其他PD读数。

[0269] 第1部分(单次递增剂量,A组和B组)结果

[0270] 十七名健康男性受试者接受了第1部分的研究药物的至少一个剂量。当在禁食状态下施用,高达200mg化合物1盐酸盐的单次口服剂量与任何生命体征、实验室安全性或心电图发现均不相关。

[0271] 化合物1血浆浓度可在2-mg剂量水平下检测到,并随着剂量的增加而增加。初步平均PK数据的汇总在表4中示出。在所施用的最高剂量水平(200mg)下,平均C_{max}=109ng/mL,平均T_{max}=3.0hr,中值t_{1/2}=3.61hr,且平均AUC_{inf}=766ng • hr/mL。

表4.

剂量 (mg)	C _{max} (ng/mL)*	SD C _{max}	T _{max} (hr)*	SD T _{max}	AUC _{inf} (hr•ng/mL)*	SD AUC _{inf}	T _{1/2} (hr) [#]
2	2.90	1.15	1.50	0.54	15.9	5.18	1.51
6	10.2	5.33	1.67	0.51	47.0	7.83	2.23
18	23.5	14.7	2.00	1.1	109	75.2	3.02
50	59.8	19.5	1.80	0.44	296	121	3.44
100 (A3)	45.7	40.0	3.17	2.56	289	185	5.82
100 (B4)	76.0	41.7	1.83	0.40	512	355	3.76
200	109	62.9	3.00	2.45	766	383	3.61

*平均值；[#]中值；A3=A组，第3时段；B4=B组，第4时段；SD=标准偏差

[0272] 如表4所示，施用100mg剂量的两个治疗时段(A组，第3时段；B组，第4时段)的血浆PK参数值的平均值和SD存在差异：A3时段的价值低于B4时段的价值，并且还与该研究的第1部分中在禁食状态下施用的所有其他剂量中所观察到的剂量相关的增加不一致。如下文所述，外周血单个核细胞(PBMC) MGLL靶标接合(TE)数据显示出A3和B4时段中类似的TE，该TE大于且不同于施用50mg剂量的B2时段中的TE。这些数据表明，A3时段的血浆PK数据是反常的。与这些PK样品的生物分析相关的实验室程序的评价并未揭示该明显反常的原因，并且出于完整性考虑，在这里报告了两个治疗时段的价值。

[0273] 从受试者收集外周血单个核细胞(PBMC)等分试样，以便以探索性方式评价对MGLL的剂量和时间依赖性的化合物1介导的抑制(也称为MGLL靶标接合(TE))。选定治疗时段的初步数据在图6中示出，其中通过水解试验测定了PBMC部分中的MGLL活性，在该水解试验中，将外源性2-花生四烯酰甘油(2-AG)添加至PBMC沉淀物，并通过质谱法将花生四烯酸(AA)的生成进行定量。基线(即，给药前)的水解活性被设置为100%。如本文所示，MGLL的抑制导致2-AG的水解以时间和剂量依赖性的方式减少。MGLL是这些条件下大部分2-AG水解的原因，但还存在一种代表已与过量化合物1预温育的PBMC沉淀物中的2-AG水解的独立于MGLL的组分，该组分的幅度在图上通过最大TE线指示。

[0274] 如图6所示，化合物1盐酸盐的口服施用与MGLL水解活性的时间和剂量依赖性抑制相关。在50mg剂量后，MGLL活性的平均最大抑制在给药后大约2小时出现，而在100mg和200mg剂量后，平均最大抑制分别在大约4-8小时和8小时出现。200mg剂量的化合物1盐酸盐与给药后大约8小时时的PBMC中MGLL的完全抑制相关，随后逐渐返回基线活性。50mg剂量的化合物1盐酸盐与总PBMC 2-AG水解活性中的大约46%的平均最大降低(对应于这次给药后大约54%的平均最大MGLL抑制)相关。

[0275] 第2部分(多次递增剂量，C-D组)结果

[0276] 不存在导致C组(10mg QD x 14天)或D组(20mg QD x 14天)中任何受试者中断的不良事件，并且生命体征、实验室测试值或ECG没有临床上显著的变化。

[0277] 对于C组和D组，在给药的第1天和第13天测量的平均化合物1血浆PK曲线分别在图

7和图8中示出。这些部分组的初步PK数据显示,化合物1血浆AUC_{0-24h}积累率(第13天/第1天)为约1.2和约1.7,并且C组和D组的血浆C_{max}积累率(第13天/第1天)分别为约1.2和约1.2。第2部分中研究药物的所有每日剂量均在禁食状态下施用。

[0278] 已完成C组和D组(两组各七名受试者)中的给药的十四名受试者的初步生物标志物(如通过PBMC介导的2-AG水解所测量的PBMC MGLL靶标接合)数据与安慰剂接受者(C组和D组合并)、化合物1盐酸盐10mg QD(C组)和20mg QD(D组)的相关初步PBMC靶标接合数据一起分别在图9、图10和图11中示出。部分完成的组的这些初步数据表明,在20mg化合物1盐酸盐每日剂量的14天后,在24小时给药间隔结束时,PBMC中的MGLL仍基本被抑制(图11)。在10mg QD剂量下,在给药第1天和第14天,给药间隔结束时的平均MGLL抑制相似,表明到给药10mg QD的化合物1盐酸盐后24小时,MGLL水解活性能够完全恢复(图10)。

实施例7. 化合物1盐酸盐对胃容受性和营养量耐受(Nutrient Volume Tolerance)的影响的单剂量、随机化、带安慰剂对照的两期交叉研究。

[0279] 该研究的主要目的在于评估化合物1盐酸盐对功能性消化不良(FD)患者的胃容受性的影响。

- 评估与安慰剂相比,化合物1盐酸盐对营养量耐受的影响;
- 评估化合物1盐酸盐在FD受试者中的安全性和耐受性;
- 评估与外周血单核细胞(PBMC)中的化合物1盐酸盐血浆浓度(例如,C_{max}、AUC₀₋₄、AUC₀₋₂₄)和单酰基甘油脂肪酶(MGLL)活性相关的IGP、营养量耐受、饱感(饱感量表,附录F)和上腹部症状(上腹部症状的VAS,附录G)的变化。

[0280] 患者:12名年龄在18至65岁之间的患有功能性消化不良和先前鉴别的胃容受性受损的成年男性或女性患者将会参加。

[0281] 标准:

入选标准:

- 患者患有由Rome III标准(附录E)定义的功能性消化不良。患者必须在过去3个月中有麻烦的餐后饱胀或早饱的主要症状,并且在筛选前至少6个月内症状发作并且没有可以解释这些症状的器官性、代谢性或全身性疾病。
- 经临床检查,基于恒压试验、具有胃内压测量的营养量耐受测试或其他类似的评价,证明患者患有胃容受性受损。该异常的证据将被记录。
- 患者的Rome III问卷结果显示,共存的上腹部疼痛和/或上腹部灼热的强度可能存在,但具有与餐后饱胀或早饱的评价相同或更低的强度(即,上腹部疼痛和灼热不是患者功能性消化不良的突出症状)。
- 患者回忆,在过去8周内的胃肠反流症状(例如,胃灼热,反胃)是每周发作不超过2次的被认为强度轻微的胃灼热或反胃。(反流疾病问卷(RDQ)将收集这些症状)
- 患者愿意在每个治疗时段之前停止影响肠道动力的特定药物至少2周。限制的药物包括阿片样物质(例如,洛哌丁胺)、多巴胺拮抗剂(例如,甲氧氯普胺、多潘立酮、阿立必利)、其他促动力剂(例如,西沙必利(cispride),替加色罗)、酸分泌抑制剂(例如,H₂拮抗剂和质子泵抑制剂,如奥美拉唑、艾美拉唑、兰索拉唑、泮托拉唑)和红霉素。
- 患者理解研究过程并且通过提供书面知情同意书同意参与该研究。
- 患者为在研究前/筛选访视时年龄为18岁至65岁的男性或女性;另外:

- 如果受试者为男性,则他应愿意在研究药物的第一次施用至研究药物的最后给药后三个月的时间内与女性性伴侣使用避孕套。

- 受试者应愿意在研究药物的第一次施用至研究药物的最后给药后三个月的时间内避免精子捐献。

- 如果受试者为绝经后的女性:受试者至少1年没有月经,并且有记录表明在研究前/筛选访视时促卵泡激素 (FSH) 水平在绝经后的范围内。

- 如果受试者为手术绝育的女性:受试者处于子宫切除术、双侧卵巢切除术或输卵管结扎术后的状态。(如果没有记录证明,则可通过超声或其他成像技术来确认子宫切除术。卵巢切除术和输卵管结扎必须由记录证实)。

- 如果受试者为具有生育能力的女性 (WOCBP),则她应同意在筛选直到最后研究访视的时间内使用两种屏障避孕方法,该方法可包括具有杀精子剂的宫颈帽、具有杀精子剂的隔膜、具有杀精子剂的避孕套或宫内避孕器 (IUD)。另外,在筛选时和在给予研究药物之前,WOCBP的尿妊娠试验应呈阴性。使用注射避孕药、植入避孕药、药环避孕药或口服避孕药的WOCBP可以参与,但必须使用一种屏障避孕方法,如具有杀精子剂的宫颈帽、具有杀精子剂的隔膜或具有杀精子剂的避孕套。

- 患者在研究前/筛选访视时具有 >18 至 $\leq 30\text{kg/m}^2$ 的身体质量指数 (BMI)。

- $\text{BMI} = \text{体重 (kg)} / \text{身高 (m)}^2$ (BMI计算应四舍五入成最接近的整数)。

- 基于在研究前/筛选时以及研究药物第一次施用前24小时内获得的病史、身体检查、生命体征测量和实验室安全性测试 (实验室发现的解释参见附录B),患者被判断为未患有不受控制的重大疾病或病症。

- 患者在研究前/筛选时以及首次施用研究药物之前的ECG没有临床上显著的异常。

- 患者不吸烟或是每天吸烟不超过2支的偶尔吸烟者,并且愿意在向临床研究单位报到之前直到完成研究程序时退出期间戒掉吸烟和含有尼古丁的产品。

- 患者愿意遵守研究限制条件。

- 患者愿意经历营养量耐受测试。

排除标准:

- 患者的年龄低于法律许可的年龄。

- 妊娠或哺乳的女性患者。

- 患者具有临床上有意义的精神病学病症 (包括严重情感障碍、焦虑症、创伤后应激障碍、精神障碍或药物引起的精神病) 的个人病史。过去曾患有具有焦虑或抑郁特征的适应性障碍的患者可由研究者决定是否可参加。

- 患者有精神分裂症、严重情感障碍、严重焦虑症或其他精神病的一级家族史。

- 患者正服用抗抑郁药,包括SSRI、SNRI、三环类抗抑郁药或非典型抗抑郁药物,如安非他酮、米氮平、曲唑酮或阿戈美拉汀。正服用这些或其他类型的针对焦虑的药物的患者也被排除。抗抑郁药已中断超过6个月的患者可由研究者决定是否可参加。正服用加巴喷丁或普瑞巴林或丁螺环酮的患者也被排除。

- 患者在精神上或法律上是无行为能力的,在研究前/筛选访视时有明显的情绪问题,或预计在研究进行中会有精神失常的可能。

- 患者具有在研究调查者看来可能混淆研究结果或可能由于参与研究而给受试者造

成额外风险的任何疾病史。

- 患者进行过任何胃肠手术。在研究前/筛选访视前已经接受阑尾切除术超过1年的那些患者可以参与。

- 患者在过去3个月内患有过任何急性胃肠疾病。

- 根据Cockcroft-Gault方程,患者的肌酐清除率(CrCl)估计值 $\leq 80\text{mL/min}$ 。如使用24小时尿液收集测量的实际肌酐清除率可替代Cockcroft-Gault计算或与Cockcroft-Gault计算结合使用。实际或计算的肌酐清除率在72-79mL/min范围内(即,在80mL/min的10%以内)的受试者可由研究者决定是否可参加。

Cockcroft-Gault方程:

$$\text{CrCl} = (140 - \text{年龄}[\text{岁}]) * (\text{体重}[\text{kg}]) / (72) \text{ 血清肌酐}[\text{mg/dL}]$$

对于女性受试者,将该值乘以0.85来获得肌酐清除率

- 受试者患有活动性神经紊乱或者有神经紊乱的既往病史,该神经紊乱包括但不限于癫痫发作、癫痫、中风、神经系统疾病、认知障碍、意识丧失延长(>10分钟)的头部创伤,或偏头痛。

- 从施用研究药物的初始剂量之前大约1周开始,经过整个研究(包括治疗时段之间的清除间隔),直到第二个治疗时段,患者无法避免或预期会使用任何药物,包括处方药和非处方药或草药(如St. John's Wort[贯叶金丝桃])。可能有某些药物是允许的。

- 患者有临床上有意义的肿瘤疾病史,经充分治疗的皮肤(例如,基底细胞癌)或宫颈的局部或原位非黑素瘤癌除外。

- 患者有显著的多重变态反应和/或严重变态反应(例如,食物、药物、乳胶变态反应)史,或者曾对方药或非处方药(包括大麻或其他含有大麻的药物)或食物有过过敏反应或显著不耐受性。

- 患者曾进行大手术、曾捐献或失去1个单位(大约500mL)的血液,或在研究前/筛选访视前4周内参与了另一项研究性试验。该4周窗口将来源于从先前试验的最后试验药物和/或血液收集和/或与试验药物相关的不良事件(AE)到当前试验的试验前/筛选访视的日期。对于曾参与未施用试验药物或未进行侵入性程序的研究性试验的患者,该间隔可被修改成不包括间隔要求。

- 患者(在研究前/筛选访视的8周内)曾进行预防性疫苗接种或计划在研究过程期间(例如,直至研究后访视)进行预防性疫苗接种。

- 患者饮用大量酒精,定义为每天>3份酒精饮料(1份大约相当于:300mL[10盎司]啤酒,125mL[4盎司]葡萄酒,25mL[1盎司]蒸馏酒)。每天饮用不超过4份酒精饮料的受试者可由研究者决定是否可参加。

- 患者消耗大量的咖啡因,定义为每天>6份咖啡、茶、可乐或其他含咖啡因的饮料(1份大约相当于120mg咖啡因)。

- 患者目前(定义为在研究前/筛选访视的大约3个月内)是任何非法药物(包括大麻)的常规使用者(包括“娱乐性使用”),或在研究前/筛选访视的大约6个月内有药物(包括酒精)滥用史。而且,患者不愿在该研究中避免使用大麻产品。

- 受试者有长QT综合征家族史。

- 受试者的QTc间隔>450msec(男性受试者)或>470msec(女性受试者)。

• 研究者担心研究中患者的安全参与,或出于任何其他原因,研究者认为受试者不适于参与该研究。

[0282] 根据计算机生成的随机码将受试者/患者随机化至交叉治疗序列A或B。

第1时段	第2时段
序列A:安慰剂	化合物1盐酸盐
序列B:化合物1盐酸盐	安慰剂

盲法:将使用随机分配计划表,通过没有收集安全性或功效数据的其他责任的非不知情药剂师制备化合物1盐酸盐或匹配的安慰剂。

[0283] 治疗持续时间:总研究参与将为大约83天,包括60天的筛选期。在两次单日治疗之间将会存在至少7天的最短清除期。应努力在第一次治疗的4周内完成第二次治疗。不使用激素避孕的WOCBP应该在两个治疗时段的每一个中在其月经周期的同一时间点进行研究。

[0284] 主要终点是化合物1与安慰剂相比,营养餐输注期间IGP随时间的变化(胃容受性)。对于每个受试者,这是从营养饮品输注开始直到其停止,从压力时间曲线与零线(大于零的值有负贡献)之间的面积计算得出的。

[0285] 其他终点包括在营养量耐受测试期间以及在营养量耐受测试之后直至压力传感器被移除的时期内随时间测量的上腹部症状的饱食评分和VAS。

实施例8:化合物1在患有阿尔茨海默病的受试者中的2期单点、随机化、双盲、带安慰剂对照的试验

[0286] 该研究的目的在于评价化合物1盐酸盐在阿尔茨海默病治疗中的安全性和功效。

[0287] 患者:合格的受试者应是40岁至95岁的男性和女性。

[0288] 标准:

入选标准:

- 可能的AD的NINCDS/ADRDA标准
- MMSE在12至27之间
- 用稳定剂量的胆碱酯酶抑制剂或NMDA (N-甲基-D-天冬氨酸) 拮抗剂治疗持续至少12

周

- 可进行家庭监测,以供药物监督
- 有照护者陪伴患者进行所有访视并且其愿意作为通知人参与研究
- 英语或西班牙语流利
- 如通过记录审查、内科医师的身体检查、神经系统检查和实验室测试确认的,对该研究有医疗稳定性

- 稳定剂量的非排除药物
- 无证据表明存在肝功能不全
- 能够吞咽口服药物
- 有能力参与知情同意过程

排除标准:

- 需要用被排除的抗糖尿病药物(参见下文)治疗的糖尿病史(OGTT标准)或低血糖史
- 活动性肝病或肾病
- 心脏疾病,包括充血性心力衰竭史或目前正对CHF进行治疗;近期心肌梗死史

- 在近两个月内使用另一种研究性药物
- 临床显著的中风史
- 癫痫或头部创伤史,近两年内有意识障碍
- 近两年内重大的精神疾病,包括精神病性障碍、双相型障碍或严重抑郁发作
- 药物排除
- 目前使用口服降血糖剂,包括磺酰脲类和美格列奈类(meglitinides)药物
- 目前或过去用胰岛素治疗超过两周
- 目前使用具有显著的抗胆碱能或抗组胺性质的药物

[0289] 研究设计:

- 分配:随机化
- 干预模型:平行指定
- 掩蔽:双盲(受试者,研究者)
- 主要目的:治疗

主要结果评价:

- 阿尔茨海默病评估量表的变化-认知分量表(ADAS-Cog)评分[时间范围:超过6个月,在第2次(第2周)、第6次(第12周)、第8次(第24周)访视时测量][指定为安全性问题:否]
- 评价记忆力、注意力、推理、语言、方向感和实践的心理测量工具。

次要结果评价:

• 阿尔茨海默病合作研究临床医师对变化的总体印象(ADCS-CCGIC)评分的变化[时间范围:超过6个月,在第2次(第2周)、第6次(第12周)、第8次(第24周)访视时测量][指定为安全性问题:否]。用于评估在独立的熟练的有经验的临床医师看来在临床试验中的临床显著的变化系统性方法。ADCS-CCGIC聚焦于从试验开始,临床医师对受试者的认知表现、功能性表现和行为表现的变化的观察。其依赖于对受试者的直接检查和对知情者的采访。与目标症状量表不同,其考虑到受试者在认知、行为和功能性活动领域的总体功能。

• 小型精神状态检查(MMSE)评分的变化[时间范围:超过6个月,在第2次(第2周)、第6次(第12周)、第8次(第24周)访视时测量][指定为安全性问题:否]。用于阿尔茨海默病药物研究的常用筛选工具。其评价方向感、记忆力、注意力、集中力、命名能力、重复能力、理解力,和构造句子以及复制两个相交的多边形的能力。

• 阿尔茨海默病合作研究日常生活活动量表(ADCS-ADL)评分的变化[时间范围:超过6个月,在第2次(第2周)、第6次(第12周)、第8次(第24周)访视时测量][指定为安全性问题:否]。ADCS-ADL评估患有阿尔茨海默病的受试者的功能性表现。以结构化访谈的形式,向受访者询问受试者在过去4周内是否尝试了量表中的每个项目以及他们的表现水平。ADCS-ADL量表很好地区分了正常对照和轻度AD患者。它具有良好的重测信度。ADCS-ADL包括来自传统的基本ADL量表的一些项目(例如,梳理、穿衣、步行、洗澡、进食、上厕所)以及来自日常生活量表的工具性活动的项目(例如,购物、做饭、使用家用电器、保持约会、阅读)。

• 神经精神量表(NPI)评分的变化[时间范围:超过6个月,在第2次(第2周)、第6次(第12周)、第8次(第24周)访视时测量][指定为安全性问题:否]。NPI是经充分验证的、可靠的多项目工具,用于基于对知情者的采访来评估AD的精神病理学和行为。

- AD生物标志物的变化[时间范围:在第2次(第2周)、第6次(第12周)、第8次(第24周)]

访视时收集血液][指定为安全性问题:否]。将从在第2次(第2周)、第6次(第12周)和第8次(第24周)访视时获得的血液样品收集血浆β-淀粉样蛋白。

• APO-E基因分型[时间范围:在第2次(第2周)访视时收集][指定为安全性问题:否]
APOe e4是AD的重要遗传风险因子。在该试验中,与许多关于AD和记忆力以及老化认知的研究一样,APOe e4等位基因将作为随时间的临床变化的预测因子被分析。

分组	指定的干预
实验组: 化合物 1 盐酸盐 患有阿尔茨海默病的受试者 干预: 药物: 化合物 1 盐酸盐	药物: 药物: 化合物 1 盐酸盐 天然产物, 见于许多食物和植物中, 有轻度的胰岛素致敏作用
安慰剂比较组: 安慰剂 患有阿尔茨海默病的受试者 干预: 药物: 安慰剂	药物: 安慰剂 患有阿尔茨海默病的受试者的安慰剂 比较

实施例9:化合物1盐酸盐在功能性胸痛患者中的研究

[0290] 美国每年诊断出约200,000例新的功能性胸痛(FCP)病例。FCP与生活质量低和医疗费用高相关。胃食管反流病(GERD)、食管动力障碍和心理障碍可导致FCP。然而,FCP的机制仍待继续探索,包括中枢和外周超敏反应以及食管壁的生物力学功能障碍。突触间隙中的CB1受体激活对神经元放电进行细调,并可实际上平息与超敏反应相关的过度兴奋。该研究的目的在于评价化合物1盐酸盐在功能性胸痛的治疗中的安全性和功效。

[0291] 患者:合格的受试者应为18岁至75岁的男性和女性。

[0292] 标准:

入选标准:

- 上个月的一周有至少一次胸痛发作。先前负面的心脏评价(EKG±非侵入性压力测试±冠状动脉造影)。动力障碍(例如:失弛缓症)和GERD的负面食管评价(正常内窥镜检查,正常24hr pH研究,或对6周的BID PPI疗法无反应)

排除标准:

- 受试者需要麻醉剂或其他止痛药物
- 受试者患有已知的GERD(除非对PPI疗法有反应并且剂量稳定)、食管炎、Barrett食管或内窥镜下消化道狭窄
- 受试者曾进行上消化道手术
- 妊娠
- 受试者患有糖尿病、神经肌肉疾病、心脏疾病或其他严重的共病(心血管、呼吸系统、肾脏、肝脏、血液、内分泌、神经系统的共病),过去两年内有癫痫或伴有意识障碍的头部创

伤的病史

- 受试者具有上呼吸道症状(如嘶哑、哮喘或喉痉挛)
- 使用药物,如巴氯芬、硫糖铝和促动力剂或任何被认为是镇静药、催眠药或精神药物的药剂

的病史

- 已知的物质滥用史
- 受试者无法同意参与
- 患者有包括躁狂症和精神分裂症在内的共病精神疾病史。当前诊断患有抑郁症或正经历抑郁症治疗的患者也将被排除

[0293] 研究设计:

- 分配:随机化
- 终点分类:安全性/功效研究
- 干预模型:平行指定
- 掩蔽:双盲(受试者,研究者)
- 主要目的:治疗

主要结果评价:

• 胸痛[时间范围:每日评估,持续12周][指定为安全性问题:否]。患者将每天填写胸痛问卷和症状的症状日记,该问卷和日记将被归一化为数值,以在各组之间比较

次要结果评价:

• 胸痛强度[时间范围:每日评估,持续12周][指定为安全性问题:否]。患者将每天填写胸痛问卷和症状的症状日记,该问卷和日记将被归一化为数值,以在各组之间比较。

• GERD症状自评量表[时间范围:基线,第2、4、8和12周][指定为安全性问题:否][时间范围:超过6个月,在第2次(第2周)、第6次(第12周)、第8次(第24周)访视时测量][指定为安全性问题:否]。患者将填写关于GERD症状的问卷,该问卷将被归一化为数值,以在各组之间比较。

- 简表36[时间范围:基线,第2、4、8和12周][指定为安全性问题:否]

检查以下8个领域的总体健康相关生活质量问卷:身体功能、身体角色功能、情绪角色功能、心理健康、活力、身体疼痛、总体健康和社交功能。

• 食管超敏反应和扩张[时间范围:基线,第4、8和12周][指定为安全性问题:否]。对食管中第一感觉、不适和疼痛的感觉阈值。反应性食管收缩的频率、振幅、曲线下面积(AUC)。

分组	指定的干预
实验组：化合物 1 盐酸盐 每隔一晚口服接受化合物 1 盐酸盐的患者	药物：化合物 1 盐酸盐 化合物 1 盐酸盐，每隔一晚，口服
安慰剂比较组：安慰剂 每隔一晚口服接受安慰剂 的患者	药物：安慰剂 安慰剂--无药物

实施例10：对化合物1盐酸盐用于多发性硬化疼痛和痉挛的3期临床研究

[0294] 本研究的目的在于评估与安慰剂相比，化合物1盐酸盐对于降低具有由多发性硬化引起的中枢性神经性疼痛和中度至重度痉挛的参与者的疼痛严重性的功效和安全性。

[0295] 患者：合格的受试者应为18岁至75岁的男性和女性。

[0296] 标准：

入选标准：

- 基于疾病诊断标准，具有由多发性硬化 (MS) 引起的中枢性神经性疼痛
- 成年男性或女性
- 每日24小时平均疼痛评分为4分或更高
- 在参加研究时，女性必须妊娠检测呈阴性
- 在至少70%的研究日完成每日日记
- 参与者可继续使用其他处方和非处方的止痛药物，只要在参加研究前1个月剂量已经稳定并且同意在整个研究中保持该稳定剂量疾病诊断标准：

o在参加研究前至少1年诊断患有MS

o在参加研究前的3个月内，疾病治疗中没有MS肿块或变化

o在参加研究前的最少3个月内，每日有由MS引起的疼痛

排除标准：

- 目前正进行MS疾病缓解疗法的临床试验
- 具有与除MS之外的病因无法明显区分的疼痛
- 任何目前或曾诊断患有躁狂症、双相型障碍、精神病或分裂情感性障碍的患者
- 有物质滥用或依赖史
- 处于妊娠或哺乳期

研究设计：

- 分配：随机化
- 终点分类：安全性/功效研究
- 干预模型：平行指定
- 掩蔽：双盲(受试者，研究者)
- 主要目的：治疗

主要结果评价：

- 第六周(急性期)的24小时平均疼痛每周评分相对于基线的变化[时间范围:基线,6周][指定为安全性问题:否]。24小时平均疼痛严重性评分每日记录在11点Likert量表上,以周平均值的形式评价,其中评分在0(无疼痛)至10(最严重的疼痛)的范围内。参与者应在每天醒来时完成电子日记。将11点Likert量表用于24小时平均疼痛的评估并以周平均值的形式评价。评分在0(无疼痛)至10(最严重的疼痛)的范围内。针对研究所在和基线严重性,调整最小二乘平均值(LS平均值)。

- 第六周痉挛NRS评分相对于基线的变化[时间范围:基线,6周][指定为安全性问题:否]。痉挛数字评级量表是0到10的患者报告的痉挛严重性的量表,其中0代表无痉挛,而10代表最严重的痉挛。

次要结果评价：

- 直至第六周(急性期)的24小时平均疼痛每周评分相对于基线的变化[时间范围:基线,6周][指定为安全性问题:否]。这是一个名义上的结果,反映了临床上重要的功效结果(相对于基线 $\geq 30\%$ 或 $\geq 50\%$ 疼痛减少)是否在终点实现。其基于在评分为0(无疼痛)至10(最严重的疼痛)的顺序量表上基线评分与终点评分之间的比较。所使用的是最近24小时内的平均疼痛严重性评分的周平均值。该周平均值基于由参与者在其日记中记录的每日评估。

- 第六周Ashworth痉挛评分相对于基线的变化[时间范围:6周][指定为安全性问题:否]。Ashworth痉挛评分是医师采用0至4的五点评分针对所测试的每个肌肉组评估的痉挛评级。

- 6周时患者对改善的总体印象量表(PGI-I)[时间范围:6周][指定为安全性问题:否]。衡量参与者对评估时相比于治疗开始时的改善的感受的量表。该评分在1(好很多)至7(差很多)的范围内。针对研究所在和基线严重性,调整最小二乘(LS)平均值。

- 第6周(急性期)短暂疼痛项目严重性和干扰评分(BPI-S/BPI-I)相对于基线的变化[时间范围:基线,6周][指定为安全性问题:否]。衡量疼痛严重性和对功能的干扰。严重性评分:每个问题0分(无疼痛)至10分(严重疼痛),评估过去24小时内的最重、最轻和平均疼痛以及当前的疼痛。干扰评分:每个问题0分(不干扰)至10分(完全干扰),评估过去24小时内的疼痛干扰,如总体活动力、心情、正常工作、与其他人的关系和睡眠。平均干扰=各个干扰项目的无缺失评分的平均值。针对研究所在和基线严重性,调整最小二乘(LS)平均值。

- 第六周(急性期)的夜间疼痛评分的周平均值相对于基线的变化[时间范围:基线,6周][指定为安全性问题:否]。夜间疼痛严重性评分的周平均值每日记录在11点Likert量表上,该量表是在0(无疼痛)至10(最严重的疼痛)的范围内的顺序量表。参与者应在每天醒来时完成电子日记。针对研究所在和基线严重性,调整最小二乘(LS)平均值。

分组	指定的干预
实验组：化合物 1 盐酸盐	药物： 药物： 化合物 1 盐酸盐 参与者在急性安慰剂对照期中接受 30 mg 化合物 1 盐酸盐 (po, QD)持续 1 周，随后在 60 mg 下接受 5 周。如果参与者完成该试验的双盲部分，则将会向参与者提供参与开放标签延长期(给予 10、20 或 40 mg QD, 持续 12 周)的选择。
安慰剂比较组： 安慰剂	药物： 安慰剂 参与者口服(po)接受安慰剂，每日一次(QD)持续 6 周(急性期)。如果参与者完成该试验的 6 周双盲部分，则将会向参与者提供参与开放标签延长期(给予 10、20 或 40 毫克[mg] QD, 持续 12 周)的选择。

实施例11：化合物1盐酸盐用于治疗炎症肠病 (IBD)

[0297] 该研究的目的在于以双盲带安慰剂对照的方式检查化合物1盐酸盐对IBD患者的疾病活动的影响。

[0298] 患者：合格的受试者应为20岁至80岁的男性和女性。

[0299] 标准：

入选标准：

- 在招募前至少三个月被诊断为患有IBD的患者将有资格参与本研究。
- 患有活动性疾病、对5ASA、类固醇或免疫调节剂具有耐药性的患者
- 克罗恩病的疾病活动指数CDAI大于200，或UC的Mayo评分高于3分。
- 年龄大于20岁

排除标准：

- 患者患有已知的精神障碍。
- 孕妇
- 患者对研究药物的任意成分敏感。
- 患者不能提供知情同意书。

- 患者在近期可能需要手术。

研究设计:

- 分配:随机化
- 终点分类:安全性/功效研究
- 干预模型:平行指定
- 掩蔽:双盲(受试者,研究者)
- 主要目的:治疗

主要结果评价:

- CDAI减少70分[时间范围:8周][指定为安全性问题:否]。

次要结果评价:

- 研究期间生活质量改变[时间范围:8周][指定为安全性问题:否]
- 研究期间任何不良事件[时间范围:8周][指定为安全性问题:是]

分组	指定的干预
实验组: 化合物 1 盐酸盐	药物: 化合物 1 盐酸盐 化合物 1 盐酸盐, 每日两次, 口服
安慰剂比较组: 安慰剂	药物: 安慰剂 安慰剂, 每日两次, 口服

实施例12:用于评价化合物1盐酸盐在偏头痛预防中的功效和安全性的随机化、双盲、带安慰剂对照、平行组、剂量反应研究

[0300] 本研究的目的在于评价与安慰剂相比,三个剂量的化合物1盐酸盐(10mg、20mg和40mg,口服)在预防偏头痛中的安全性和功效。

[0301] 患者:合格的受试者应为18岁至65岁的男性和女性。

[0302] 标准:

入选标准:

• 在研究前至少6个月内,与根据国际头痛协会(IHS)的有或没有先兆的偏头痛一致的病史

- 在基线阶段,每月3至12个偏头痛期并且不超过15个头痛日(偏头痛和非偏头痛)
- 在基线时的神经检查、心电图(ECG)或临床实验室测试结果没有临床上显著的异常
- 女性患者必须绝经后至少1年、手术绝育、实行禁欲或实行可接受的避孕方法(要求妊娠测试呈阴性)

排除标准:

- 患者患有除偏头痛之外的头痛
- 患者患有发作性紧张或窦性头痛
- 50岁之后发生偏头痛
- 患者有超过两个适当的偏头痛预防方案失败

- 患者过度使用止痛药物或某些其他药物

研究设计:

- 分配:随机化
- 终点分类:安全性/功效研究
- 干预模型:平行指定
- 掩蔽:双盲(受试者,研究者)
- 主要目的:治疗

主要结果评价:

• 疼痛性偏头痛症状(偏头痛期)的发生至停止之间的时间长度相对于基线的变化。在整个研究中进行安全性评价。

次要结果评价:

• 对治疗有反应的患者比例。从基线至双盲期,每月偏头痛发作次数、每月偏头痛天数、需要急救药物的天数/月数和健康相关生活质量量度的变化。

[0303] 这是一项随机化、双盲、带安慰剂对照、平行组、多中心研究,用于评价三个不同剂量的化合物1盐酸盐(10mg、20mg和40mg,每日)在偏头痛预防中的有效性和安全性。该研究由五个阶段组成:基线(确定患者是否满足合格标准并逐渐减少患者已经在服用的任何偏头痛药物);初始滴定和双盲阶段(8周),从5mg/每日开始增加至指定剂量(10、20和40mg/日的化合物1盐酸盐);随后为在目标剂量下的维持期(18周);递减过渡阶段(最多7周);调整剂量以使有效性最大化并使副作用最小化。主要的研究假设如下:基于每月(28天)偏头痛期比例从预期基线期至双盲阶段的变化,三个剂量的化合物1盐酸盐(10、20和40mg/日)中的一个或多个在偏头痛预防方面将优于安慰剂,并且化合物1盐酸盐治疗被良好耐受。在滴定期(8周)期间,剂量被提高至化合物1盐酸盐(10、20和40mg)或安慰剂的目标每日剂量,每日常口服用两次。剂量持续18周,经7周调整,并在开放标签延长期中持续最长6个月。

实施例13:化合物1盐酸盐在治疗患有由囊肿切除术引起的急性疼痛的患者中的研究

[0304] 本研究的目的在于评价化合物1盐酸盐对囊肿切除术中的疼痛的效果。

[0305] 患者:合格的受试者应为20-80岁的男性和女性。

[0306] 标准:

入选标准:

- 正经历初步的单侧第一跖骨囊肿切除术(仅包括有或没有Akin程序的远端Chevron截骨术)的患者
- 基于筛选时进行的临床实验室测试,是健康的或医学上稳定的。如果结果在正常参考范围以外,则仅在研究者判断出对于研究中的群体,异常或相对于正常的偏差在临床上不显著或是合适且合理的情况下才可包含该患者。
- 如果女性在参加前和整个研究中是性活跃的,则其必须是绝经后的、手术绝育的、禁欲的,或实行或同意实行有效的节育方法。有生育能力的女性必须在筛选时血清 β 人绒毛膜促性腺激素妊娠测试呈阴性,且在手术前尿液妊娠测试呈阴性。
- 如果为男性并且是性活跃的,则其应同意使用批准的节育方法以防止其女性伴侣怀孕,且应同意自首次研究药物服用日起直到最后研究药物服用日之后的3个月内不捐献精子。为了有资格进入双盲治疗期,必须符合下列标准:

- 合格的基线疼痛强度 (PI) 必须在随机化前30分钟内记录的11点 (0至10) PI数字评级量表 (NRS) 上被评级为大于或等于4。

- 合格PI的出现必须不得早于第一次手术切口后10小时

- 合格的基线PI必须在术后手术期间全身镇痛结束后9小时内出现

- 排除标准:

- 癫痫发作或癫痫病史,显示在筛选前1年内出现轻度或中度创伤性脑损伤、中风、短暂性脑缺血发作或脑肿瘤,和/或筛选前15年内出现严重创伤性脑损伤、持续超过24小时意识不清,或持续超过24小时的创伤后遗忘症

- 研究开始前2年内的恶性肿瘤史

- 有证据表明存在可扩散至体内其他区域的活动性感染,或1型或2型人免疫缺陷病毒史

- 临床实验室值反映出严重肾功能不全

- 中度或严重肝功能损伤,或患者丙氨酸转氨酶或天冬氨酸转氨酶异常

- 在研究者看来,临床实验室值在手术的可接受限度之外

- 在研究者看来,可能影响功效或安全性评估的临床显著的疾病

- 在随机化前2周内用抗惊厥药、单胺氧化酶抑制剂、三环类抗抑郁药、神经安定药或血清素去甲肾上腺素再摄取抑制剂进行过治疗

- 筛选前4周内进行过全身性类固醇治疗,吸入式或局部类固醇除外

- 计划在研究期间怀孕的女性,或哺乳期女性

研究设计:

- 分配:随机化

- 终点分类:功效研究

- 干预模型:平行指定

- 掩蔽:双盲 (受试者,研究者)

- 主要目的:治疗

主要结果评价:

- 48小时内疼痛强度差异总和 (SPID) [时间范围:48小时] 在0到10的11点数字评级量表上评估强度 (PI), 其中0=无疼痛而10=难以想象的疼痛。PID是评估时基线PI (第一剂量前) 与当前PI之间的差异。SPID以48小时内PID评分的时间加权总和计算。对于SPID48,总分在-480 (最差) 至480 (最好) 的范围内。较高的SPID值表示更好的疼痛缓解。

次要结果评价:

- 第一次使用急救药物的时间 [时间范围:最长48小时] [指定为安全性问题:否]

- 12、24、48和72小时时的疼痛强度相对于基线的降低 [时间范围:基线 (第1天) 和第12、24、48和72小时] [指定为安全性问题:否]

[0307] 这是一项随机化、双盲 (医师和患者都不知道指定药物的名称)、安慰剂对照、平行组、多中心研究,用于评价25mg和50mg化合物1盐酸盐在正经历囊肿切除术 (用于移除囊肿的手术程序) 的患者中的功效和安全性。本研究将分为筛选期、手术期、定量期和双盲治疗期。包括筛选期在内的研究长度将会最多长达32天。以1:1:1的比例将有资格的患者随机分配至3个治疗组 (化合物1盐酸盐25mg、化合物1盐酸盐50mg或安慰剂) 中的1个。功效和安全

性评估将在研究期间进行。

实施例14:阿片样物质在有或没有化合物1盐酸盐的情况下用于治疗具有中度至重度癌症疼痛的患者

[0308] 本研究的目的在于观察阿片样物质在与或不与化合物1盐酸盐一起给予的情况下治疗具有中度至重度癌症疼痛的患者的效果如何。

[0309] 患者:合格的受试者应为18-70岁的男性和女性。

[0310] 标准:

- 中度至重度癌症疼痛
- 疼痛评分 $\geq 7/10$ (0-10数字疼痛评级量表)
- 需要强力阿片样物质 (第3步) 来控制疼痛,或已经处于第3步稳定剂量的阿片样物质下
- 阿片样物质造成认知功能障碍或认知损害
- 预期寿命 ≥ 3 个月
- 肾功能正常
- 未妊娠或哺乳
- 妊娠测试呈阴性
- 必须有电话
- 能够单独或在辅助下完成患者问卷
- 无精神错乱
- 无肝功能障碍
- 非养老院患者
- 无难治性恶心或呕吐
- 对阿片样物质无真正过敏或不耐受
- 没有影响阿片样物质吸收的胃肠病理学
- 无觅药行为或近期物质滥用史
- 无重度抑郁
- 无呼吸系统损伤
- 无证据表明存在严重或不受控制的全身性疾病 (例如,不稳定或非代偿性呼吸系统、心脏、肝脏或肾脏疾病)
- 无证据表明存在使患者不宜参与研究的任何其他显著的临床病症或实验室发现
- 距先前放疗、化疗或放射性核素超过1个月
- 距先前二膦酸盐超过1个月
- 没有影响阿片样物质吸收的先前手术
- 没有同时进行影响疼痛的治疗程序或治疗
- 没有同时进行主动放疗或抗肿瘤疗法
- 没有同时进行逆转录病毒疗法
- 没有同时服用干扰CYP3A4、CYP1A2或CYP2D6的药物
- 没有同时服用干扰吗啡代谢的药物
- 没有同时服用将会影响吗啡或美沙酮处置的药物

- 没有同时服用其他止吐药、抗焦虑药或神经安定剂

研究设计:

- 分配:随机化
- 掩蔽:双盲(受试者,研究者)
- 主要目的:支持性照护

主要结果评价:

- 相对于基线的两点疼痛改善(0-10数字疼痛评级量表)[指定为安全性问题:否]。

次要结果评价:

- 主动治疗与安慰剂的比较[指定为安全性问题:否]
- 化合物1盐酸盐对阿片样物质副作用的影响[指定为安全性问题:否]
- 终点之间的关系[指定为安全性问题:否]

分组	指定的干预
主动比较组: 组 I 患者接受口服阿片样物质和口服安慰剂, 每日一次, 持续 4 周	其他: 安慰剂 口服给予
实验组: 组 II	药物: 化合物 1 盐酸盐
患者接受口服阿片样物质和 50 mg 口服化合物 1 盐酸盐, 每日一次, 持续 4 周	口服给予
实验组: 组 III 患者接受口服阿片样物质和 100 mg 口服化合物 1 盐酸盐, 每日一次, 持续 4 周	药物: 化合物 1 盐酸盐 口服给予

实施例15:化合物1盐酸盐用于治疗骨关节炎疼痛的研究

[0311] 本研究的目的在于评价化合物1盐酸盐对臀部或膝盖的骨关节炎疼痛的效果。

[0312] 患者:合格的受试者应为超过40岁的男性和女性。

[0313] 标准:

入选标准:

- 基线时初步诊断患有臀部或膝盖的功能性I-III级OA,具有记录的骨关节炎突发
- 非甾体抗炎药(NSAID)和/或醋氨酚用于OA疼痛的长期使用者
- 在筛选时中断所有镇痛疗法
- 对于有生育能力的女性:未妊娠且未哺乳的女性,以及实行可接受的节育方法的女性

• 排除标准:

- 需要持续使用阿片样物质或阿片样物质组合产品来控制膝盖或臀部的OA疼痛
- 临床上明显不稳定的心脏、呼吸系统、神经系统、免疫性、血液或肾脏疾病
- 吞咽胶囊有重大困难或不能忍受口服药物
- 在筛选前30天内曾参与另一项关于化合物1盐酸盐的临床研究或接受任何研究性药物或装置或研究性疗法

研究设计:

- 分配:随机化
- 终点分类:安全性/功效研究
- 干预模型:平行指定
- 掩蔽:双盲(受试者,研究者)
- 主要目的:治疗

主要结果评价:

• 在西安大略和麦克马斯特大学骨关节炎指数(WOMAC)疼痛分量表评分上测量的骨关节炎疼痛从基线至进入试验后第12周的变化。[时间范围:基线至第12周/提前终止][指定为安全性问题:否]。采用西安大略和麦克马斯特大学骨关节炎指数(WOMAC)疼痛分量表评分来测量患有骨关节炎的受试者的疼痛。WOMAC疼痛分量表评分来自5个疼痛分量表问题的视觉模拟量表(VAS)评分的平均值计算。受试者对VAS进行标记,该VAS是长度为100mm的水平线,带有指示过去24小时内其疼痛水平的单根竖线,其中0mm表示“无疼痛”而100mm表示“极度疼痛”。WOMAC疼痛分量表评分差异以在第12周评估的WOMAC疼痛分量表评分减去在基线时评估的WOMAC疼痛分量表评分来计算。

次要结果评价:

- 在西安大略和麦克马斯特大学骨关节炎指数(WOMAC)疼痛分量表评分上测量的骨关节炎疼痛从基线至进入试验后第2周的变化
- 在西安大略和麦克马斯特大学骨关节炎指数(WOMAC)疼痛分量表评分上测量的骨关节炎疼痛从基线至进入试验后第6周的变化
- 在西安大略和麦克马斯特大学骨关节炎指数(WOMAC)疼痛分量表评分上测量的骨关节炎疼痛从基线至进入试验后第2、6和12周的平均值的变化

分组	指定的干预
实验组: 化合物 1 盐酸盐 25 mg, 每日两次	药物: 化合物 1 盐酸盐 25 mg, 每日两次
实验组: 化合物 1 盐酸盐 25 mg, 每日三次	药物: 化合物 1 盐酸盐 25 mg, 每日三次
安慰剂比较组: 安慰剂	药物: 安慰剂

实施例16:比较两个剂量的化合物1盐酸盐与安慰剂用于类风湿性关节炎治疗的3期研究

[0314] 本研究的目的在于评价化合物1盐酸盐对改善类风湿性关节炎患者的体征和症状以及身体功能的效果。

[0315] 患者:合格的受试者应为超过40岁的男性和女性。

[0316] 标准:

入选标准:

- 基于美国风湿病学会 (ACR) 1987年修订的标准,患者被诊断患有RA。
- 患者在筛选和基线时都患有活动性疾病,该活动性疾病如下定义:运动时 ≥ 6 处关节触痛或疼痛;以及 ≥ 6 处关节肿大;并且筛选时满足以下2个标准中的1个:1.在当地实验室中ESR (韦斯特格伦法) $> 28\text{mm}$ 。2.在中心实验室中CRP $> 7\text{mg/L}$
- 由于缺乏功效或毒性,患者对至少一种DMARD (传统或生物的) 的反应不足。
- 无证据表明存在活动性或潜伏性或未充分治疗的结核分枝杆菌 (*Mycobacterium tuberculosis*) 感染。
- 除了抗疟药之外,患者已经清除了所有DMARD

排除标准:

- 包括经确认的以下各项的血液恶液质:1.血红蛋白 $< 9\text{g/dL}$ 或血细胞比容 $< 30\%$;2.白细胞计数 $< 3.0 \times 10^9/\text{L}$;3.绝对嗜中性粒细胞计数 $< 1.2 \times 10^9/\text{L}$;4.血小板计数 $< 100 \times 10^9/\text{L}$
- 除舍格伦综合征外的任何其他自身免疫性风湿性疾病史
- 无恶性肿瘤或恶性肿瘤史
- 在研究药物第一次给药前6个月内,需要住院、肠胃外抗菌疗法的感染史,或如研究者以其他方式判断为临床上显著的感染史

研究设计:

- 分配:随机化
- 终点分类:安全性/功效研究
- 干预模型:平行指定
- 掩蔽:双盲 (受试者,研究者)
- 主要目的:治疗

主要结果评价:

• 在第3个月实现美国风湿病学会20% (ACR20) 反应的参与者的百分比 [时间范围:第3个月] [指定为安全性问题:否]。ACR20反应:触痛关节计数改善大于或等于 ($\geq$) 百分之20 (%);肿大关节计数改善 $\geq 20\%$;以及以下5种剩余ACR核心量度中至少3种的改善 $\geq 20\%$:参与者对疼痛的评估;参与者对疾病活动的总体评估;医师对疾病活动的总体评估;自我评估的残疾 (健康评估问卷 [HAQ] 的残疾指数);和C-反应蛋白 (CRP)。

• 第3个月的健康评估问卷-残疾指数 (HAQ-DI) 评分相对于基线的变化 [时间范围:基线,第3个月] [指定为安全性问题:否]。HAQ-DI:过去一周执行以下8个功能类别的日常生活活动中的任务的能力的参与者报告的评估:穿衣/梳理;起立;进食;步行;伸手;紧握;卫生;以及常见活动。每项以0-3的4点量表评分:0=没有困难;1=有些困难;2=非常困难;3=无法做到。总分以领域评分总和计算并除以回答的领域数。可能的总分在0-3的范围内,0=功

能难度最低,而3=功能难度极大。

- 在第3个月,采用28关节计数和红细胞沉降率(4个变量)(DAS28-4[ESR])进行的疾病活动评分低于2.6的参与者百分比[时间范围:第3个月][指定为安全性问题:否]。由采用28关节计数的肿大关节计数(SJC)和触痛/疼痛关节计数(TJC)、红细胞沉降率(ESR)(毫米每小时[mm/小时])和患者对疾病活动的总体评估(PtGA)(经转换的评分在0至10范围内;分数越高表示由于疾病活动而产生的假象越大)来计算DAS28-4(ESR)。总分在0至9.4范围内,分数越高表示疾病活动度越高。DAS28-4(ESR)小于或等于($\leq$)3.2意味着较低的疾病活动度,大于($>$)3.2至5.1意味着中度至极高的疾病活动度,而小于($<$)2.6=缓解。

次要结果评价:

- 在第2周、第1和2个月达到美国风湿病学会20%(ACR20)反应的参与者的百分比[时间范围:第2周、第1和2个月][指定为安全性问题:否]。
- 在第4、5和6个月达到美国风湿病学会20%(ACR20)反应的参与者的百分比[时间范围:第4、5和6个月][指定为安全性问题:否]。
- 在第2周、第1和2个月达到美国风湿病学会50%(ACR20)反应的参与者的百分比[时间范围:第2周、第1和2个月][指定为安全性问题:否]。
- 在第4、5和6个月达到美国风湿病学会50%(ACR20)反应的参与者的百分比[时间范围:第4、5和6个月][指定为安全性问题:否]。

分组	指定的干预
实验组: 化合物 1 盐酸盐 10 mg	药物: 化合物 1 盐酸盐 10 mg 化合物 1 盐酸盐, 每日两次, 口服, 持续 6 个月
实验组: 化合物 1 盐酸盐 25 mg	药物: 化合物 1 盐酸盐 25 mg 化合物 1 盐酸盐, 每日两次, 口服, 持续 6 个月
安慰剂比较组: 安 慰剂序列 1	药物: 安慰剂 在第 3 个月访视时安慰剂患者发展至 10 mg 化合物 1 盐酸盐, 每日两次
安慰剂比较组: 安 慰剂序列 2	药物: 安慰剂 在第 3 个月访视时安慰剂患者发展至 25 mg 化合物 1 盐酸盐, 每日两次

实施例17: 化合物1盐酸盐在治疗患有化疗引起的周围神经病变的患者中的效果

[0317] 本研究的目的在于评估效果,以测试在6周治疗后化合物1盐酸盐对周围神经病变评分的影响,并且该研究是基于疼痛和感觉迟钝评分的单独评估。

[0318] 患者:合格的受试者应为18-80岁的男性和女性。

[0319] 标准:

[0320] 入选标准:

- 已在任何研究相关的程序进行前签署了参与试验的知情同意书。
- >18岁,并且若有生育能力的女性,应采取充分避孕
- 如通过NCI-CTC第2版神经病感觉等级 ≥ 2 的存在评估的,患有紫杉醇(或其他紫杉烷)引起的周围神经病变。
- 如神经系统检查(包括敏感性、运动功能和深腱反射评估)期间临床诊断的周围神经病变
- 具有如通过在筛选访视时在Likert数字评级量表上 ≥ 4 的可测量的疼痛感(前24h)的存在评估的并且在DN4上确认评分 ≥ 4 的神经性疼痛,并且/或者具有如通过在筛选访视时在Likert数字评级量表上 ≥ 4 分的可测量的感觉迟钝(前24h)的存在评估的感觉迟钝
- 化疗结束后持续至少3个月但不超过12个月的持续性神经病。
- 未经疼痛治疗,或其当前的止痛药(在前一个月内稳定)有重大副作用或缓解不充分。

排除标准:

- 有记录证明存在神经病或可能干扰疼痛严重性评估的神经病风险因素(例如,包括但不限于2型糖尿病、外周血管疾病、B12维生素缺乏症、甲状腺功能障碍、外科手术后神经性疼痛、创伤后神经病或与疾病进展有关的神经病)。
- 患有可能会导致虚弱、感觉丧失或自主神经症状或实验室检查异常的其他神经疾病。
- 治疗难治性的,定义为在研究者看来,通过3次或更多次针对当前PN症状进行的治疗而没有改善。
- HIV血清学呈阳性。
- 当前患有心脏节律失常或有心脏节律失常史,和/或有包括心肌梗死在内的心血管疾病史,仅患有良好控制的高血压的患者除外。
- 曾服用(过去6个月内)或同时服用神经毒性药物(例如,但不限于顺铂、长春新碱、长春花碱、阿糖胞苷、沙利度胺、硼替佐米或丙卡巴肼、卡培他滨、诺维本)。
- 当前服用除他汀类药物以外的降脂剂药物。
- 近期有酗酒或药物滥用史(前6个月内),或当前有证据表明酗酒或药物滥用。
- 患有涉及任何系统的并发不稳定疾病(例如,除近期用紫杉烷治疗有效的癌之外的晚期癌,心肌梗死、心肌缺血的临床或ECG征兆、心功能不全、心绞痛症状、当前CAD症状、肾损伤或在研究者看来会使患者不适于参与研究的任何其他病况)。
- 妊娠或哺乳期女性。
- 具有肾损伤,定义为血肌酐 $>1.5 \times$ 正常值上限(ULN)。
- 止血障碍或当前用口服抗凝剂治疗。

- 具有如下的肝功能受损:在肝转移情况下肝酶 (ALT和AST) $>2 \times \text{ULN}$ 或 $>3.5 \times \text{ULN}$ 。
- 在过去3个月内参与任何其他研究性药物研究或利用未批准药物的疗法研究。
- 在研究者看来,会妨碍胜任性或依从性或可能阻碍研究完成的任何其他病况。

研究设计:

- 分配:随机化
- 终点分类:安全性/功效研究
- 干预模型:平行指定
- 掩蔽:双盲(受试者,研究者)
- 主要目的:治疗

主要结果评价:

• 反应者的百分比,该反应者定义为基线时存在的最大神经性疼痛尺度(疼痛或感觉迟钝)下降最少50%的患者。[时间范围:治疗期的最后7天的平均疼痛评分将会与筛选评分期的最后7天的平均评分相比较。][指定为安全性问题:否]。

次要结果评价:

• 评估相对于安慰剂,化合物1盐酸盐对神经性疼痛量表评分(总分和按尺度评分)的影响[时间范围:筛选访视;V0;V1;V2;V3;V4;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对简表BPI的影响[时间范围:筛选访视;V0;V1;V2;V3;V4;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对生活质量问卷(CIPN 20)的影响[时间范围:V0;V3;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对味觉障碍问卷的影响[时间范围:V0;V3;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对定量感觉测试的影响[时间范围:V0;V3;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对ENMG的影响[时间范围:V0;V3;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对急救药物使用的影响[时间范围:筛选访视;V0;V1;V2;V3;V4;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对安全性特性的影响[时间范围:筛选访视;V0;V1;V2;V3;V4;V5][指定为安全性问题:是]。

• 评估相对于安慰剂,化合物1盐酸盐对由研究者评估的总体印象变化的影响[时间范围:V1;V2;V3;V4;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对由患者评估的总体印象变化的影响[时间范围:V1;V2;V3;V4;V5][指定为安全性问题:否]。

• 评估相对于安慰剂,化合物1盐酸盐对医院焦虑抑郁量表的影响[时间范围:V0;V3;V5][指定为安全性问题:否]。

分组	指定的干预
实验组：化合物 1 盐酸盐 (40 mg)，每日一次	药物：化合物 1 盐酸盐 化合物 1 盐酸盐 (40 mg)，每日一次
安慰剂比较组：对照 安慰剂，每日一次	药物：安慰剂对照 安慰剂，每日一次

占据率%与剂量

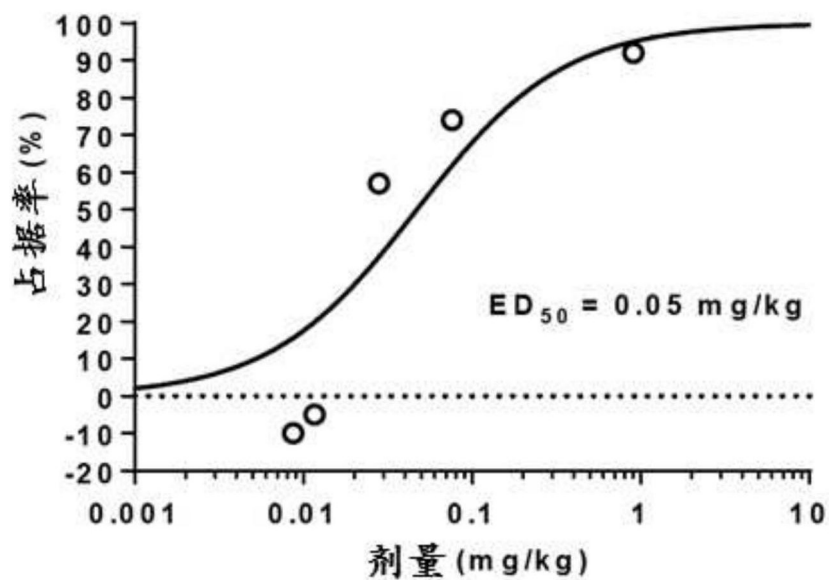


图1

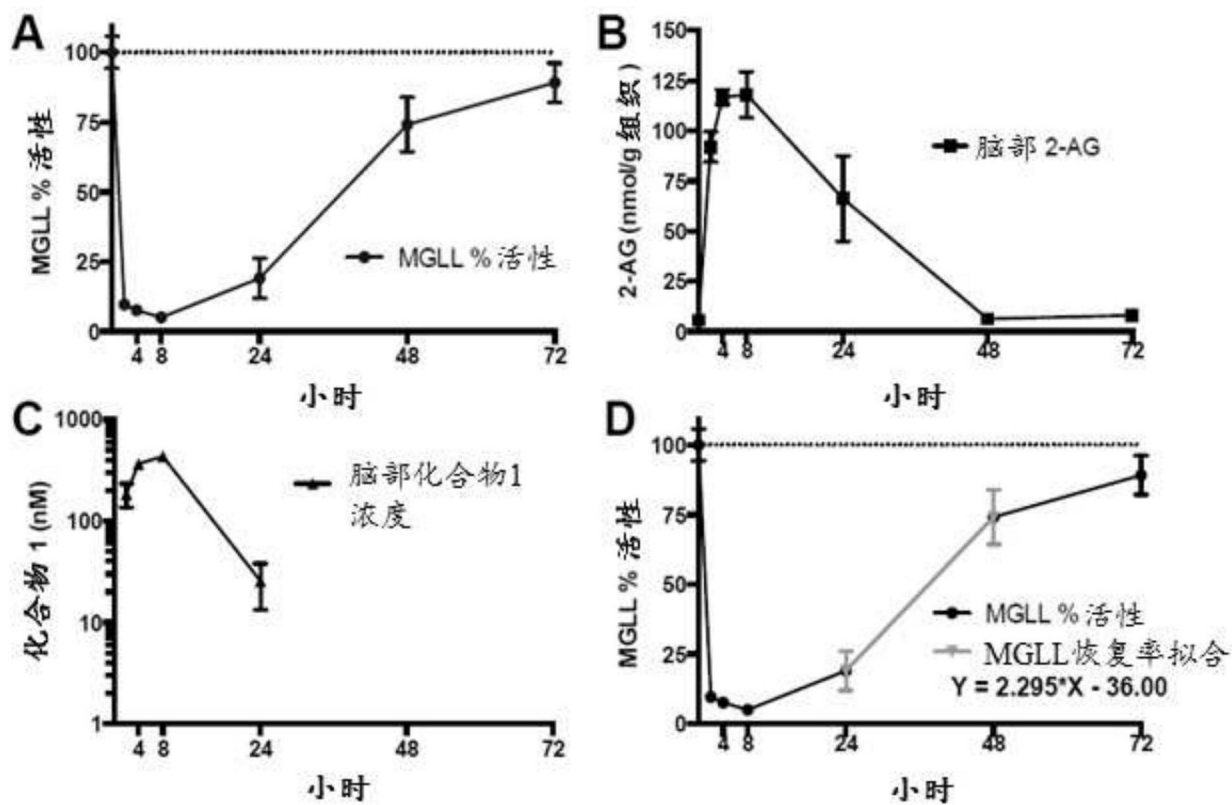


图2

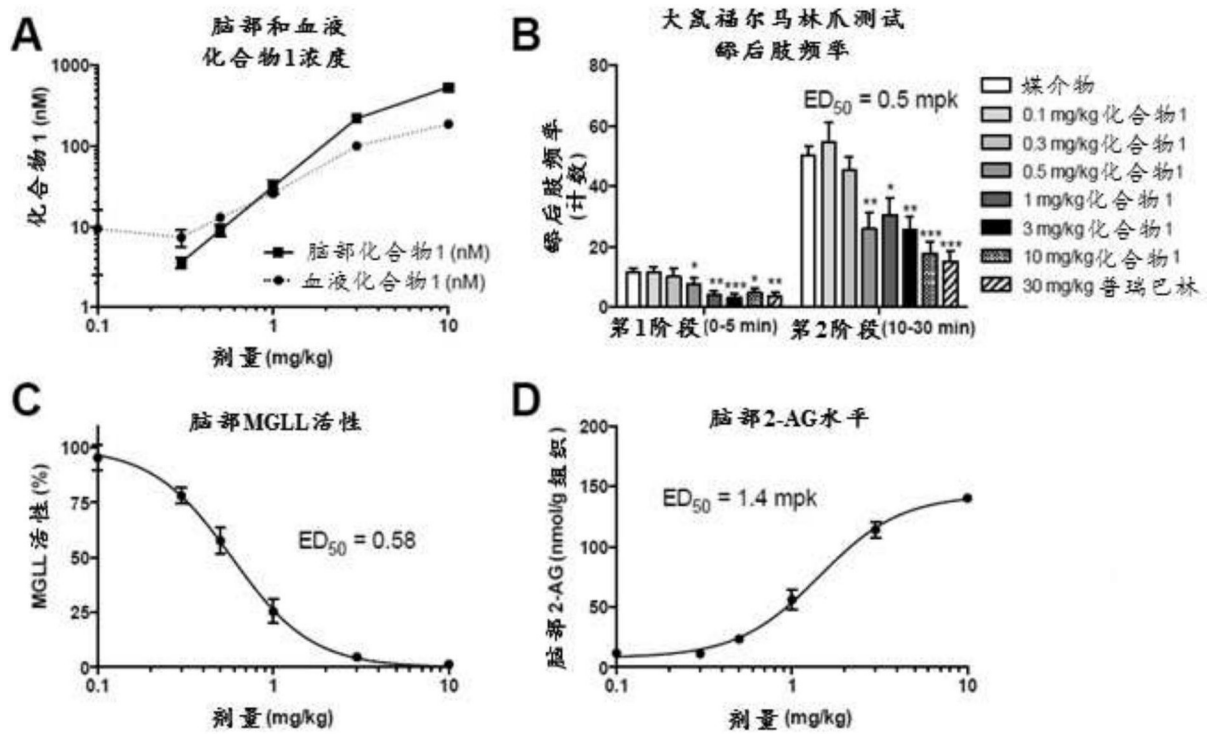


图3

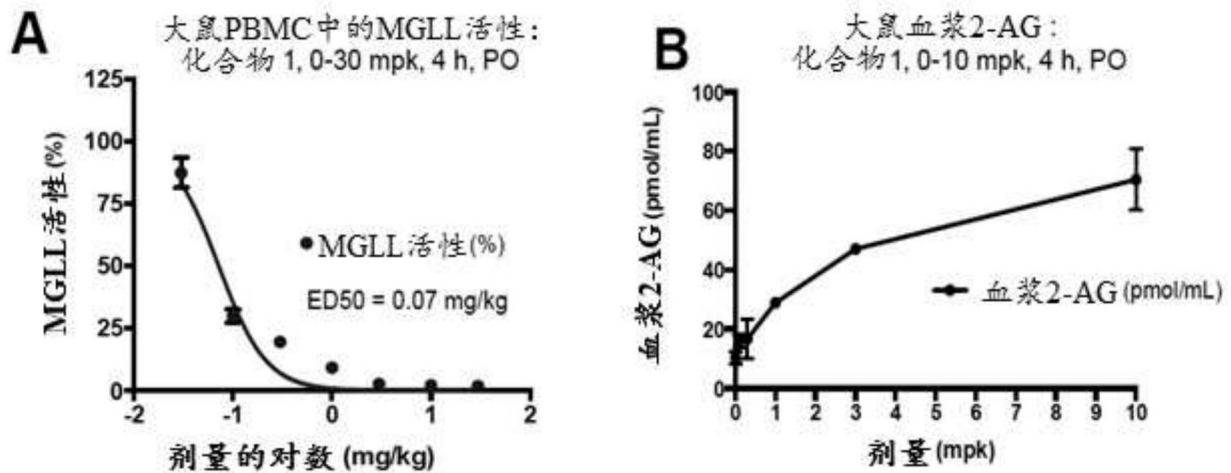


图4

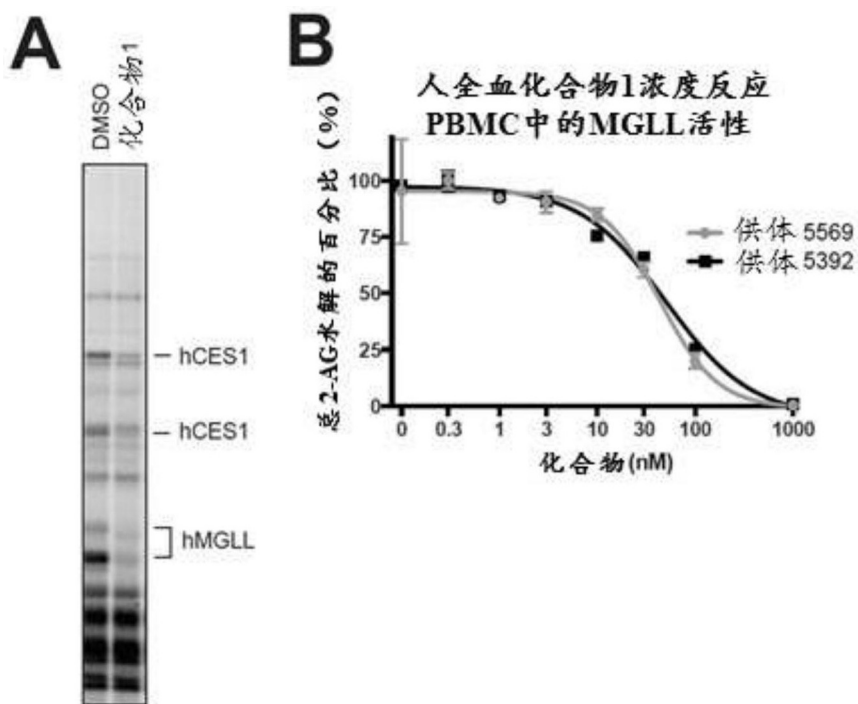


图5

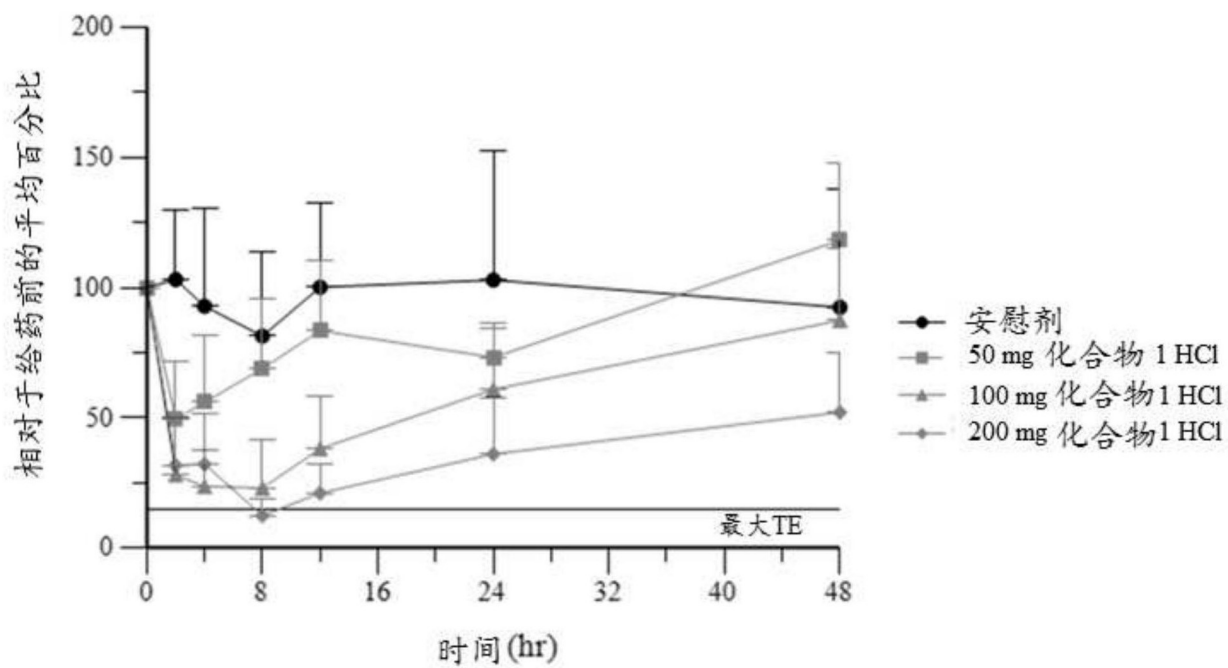


图6

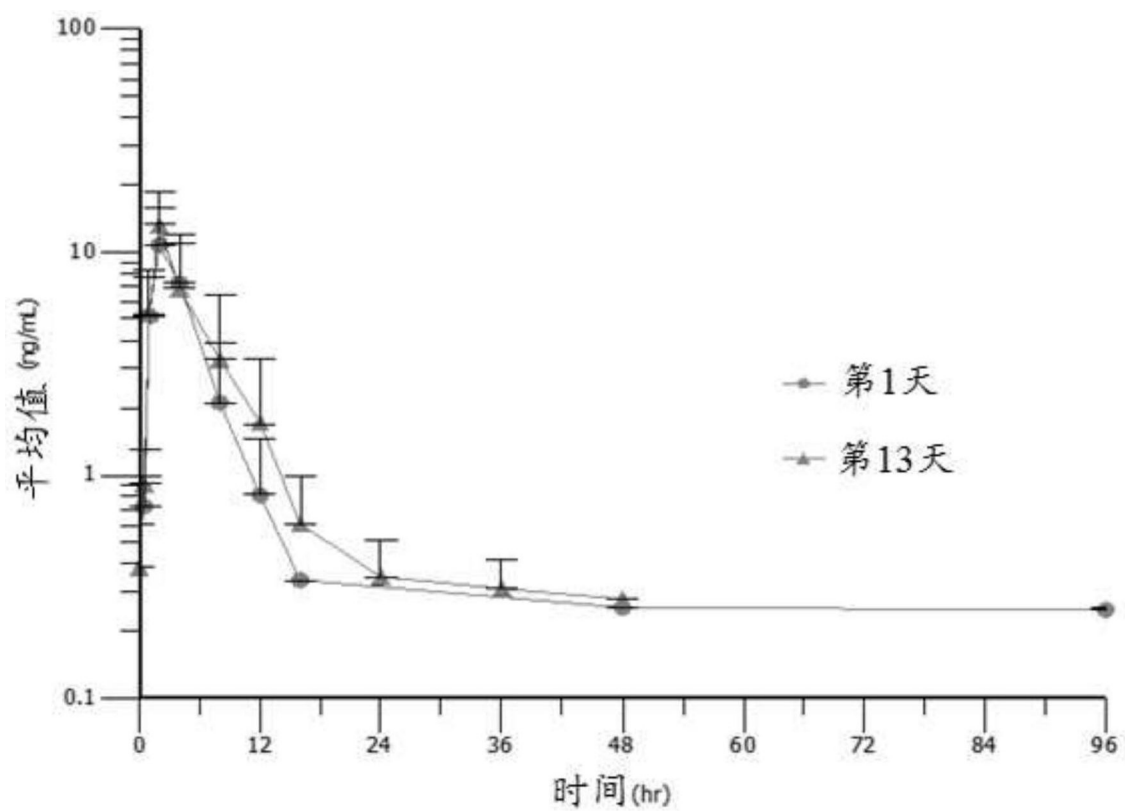


图7

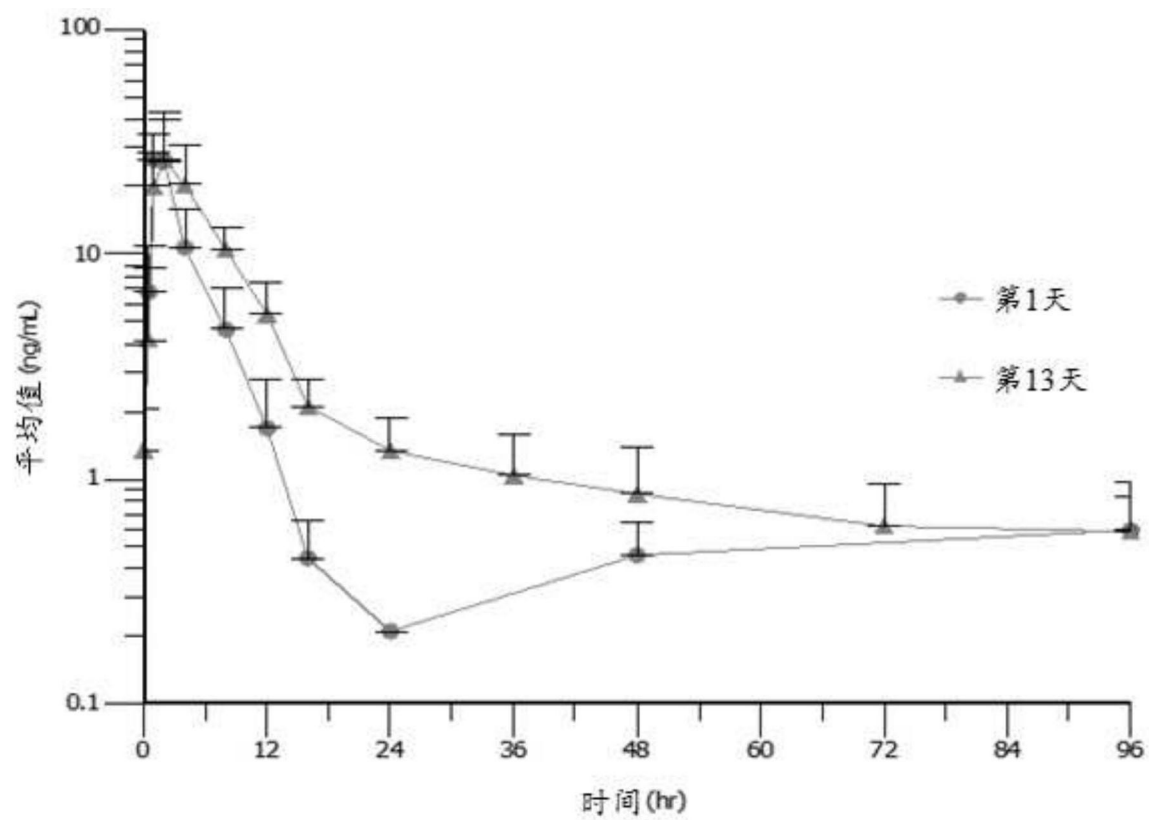


图8

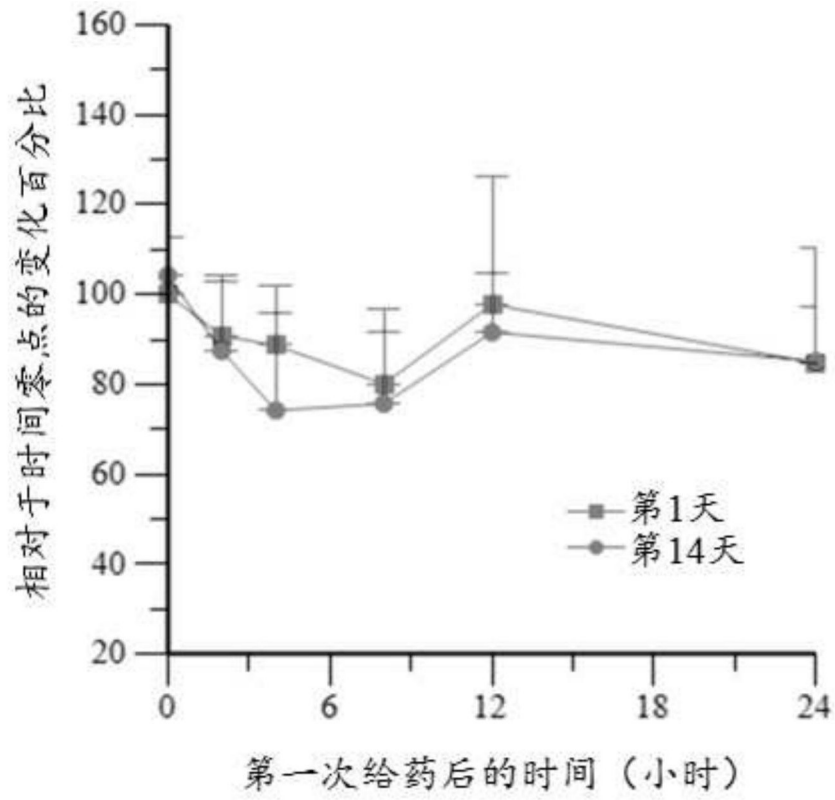


图9

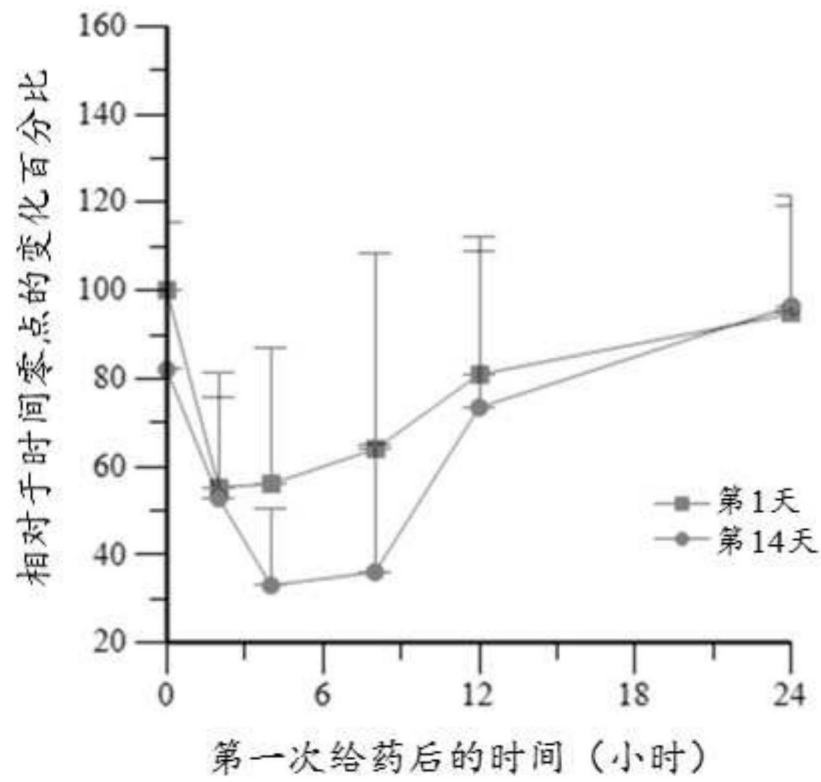


图10

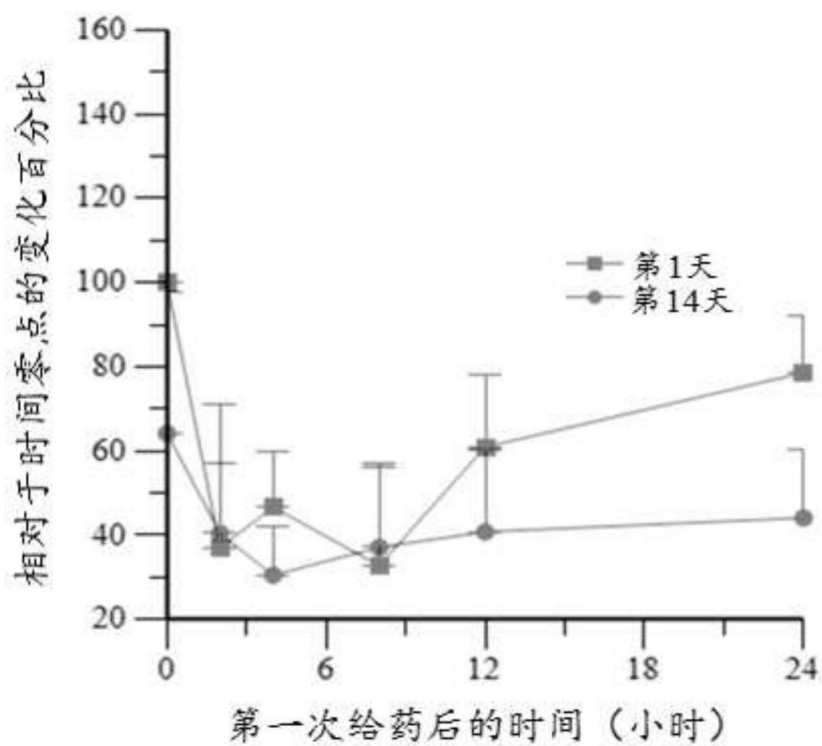


图11