(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
03 September 2020 (03.09.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/176763 A1

(51) International Patent Classification:
A61K 9/48 (2006.01) *A61P 29/00* (2006.01)
A61K 31/435 (2006.01)

(21) International Application Number:
PCT/US2020/020159

(22) International Filing Date:
27 February 2020 (27.02.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/811,260 27 February 2019 (27.02.2019) US

(71) Applicant: **VERTEX PHARMACEUTICALS INCORPORATED** [US/US]; 50 Northern Avenue, Boston, MA 02210 (US).

(72) Inventor: **MILLER, Jonathan**; 50 Northern Avenue, Boston, MA 02210 (US).

(74) Agent: **SHEREDA, Robert, D.** et al.; Barnes & Thornburg LLP, 24 Frank Lloyd Wright Dr., Suite A-3300, P.O. Box #511, Ann Arbor, MI 48105 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, 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).

Published:
— *with international search report (Art. 21(3))*

(54) Title: DOSAGE FORM COMPRISING PRODRUG OF NA 1.8 SODIUM CHANNEL INHIBITOR

(57) Abstract: Described herein are pharmaceutical compositions of a pyridone amide prodrug sodium channel inhibitor (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2oxopyridin-1(2H)-yl)methyl dihydrogen phosphate, dosage forms thereof, and methods for manufacturing and administering the compositions for the treatment of various types of pain.

WO 2020/176763 A1

DOSAGE FORM COMPRISING PRODRUG OF NA 1.8 SODIUM CHANNEL INHIBITOR

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application Serial No. 62/811,260, filed February 27, 2019, the entire contents of which is incorporated herein by reference.

TECHNICAL FIELD

[0002] Described herein are pharmaceutical compositions of a pyridone amide prodrug sodium channel inhibitor (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate, and salts thereof, dosage forms thereof, and methods for manufacturing and administering the compositions for the treatment of various types of pain.

BACKGROUND

[0003] Pain is a protective mechanism that allows healthy animals to avoid tissue damage and to prevent further damage to injured tissue. Nonetheless, there are many conditions where pain persists beyond its usefulness, or where patients would benefit from inhibition of pain. Neuropathic pain is a form of chronic pain caused by an injury to the sensory nerves. Dieleman et al., Incidence rates and treatment of neuropathic pain conditions in the general population, *Pain* 137(3): 681-688 (2008). Neuropathic pain can be divided into two categories, pain caused by generalized metabolic damage to the nerve, and pain caused by a discrete nerve injury. The metabolic neuropathies include post herpetic neuropathy, diabetic neuropathy, and drug-induced neuropathy. Discrete nerve injuries indications include post amputation pain, post-surgical nerve injury pain, and nerve entrapment injuries like neuropathic back pain.

[0004] Voltage-gated sodium channels (Navs) play a critical role in pain signaling. Navs are key biological mediators of electrical signaling, as they are the primary mediators of the rapid upstroke of the action potential of many excitable cell types (e.g., neurons, skeletal myocytes, and cardiac myocytes). The evidence for the role of these channels in normal physiology, the pathological states arising from mutations in sodium channel genes, preclinical work in animal models, and the clinical pharmacology of known sodium channel modulating agents all point to the central role of

Navs in pain sensation. Rush and Cummins, Painful Research: Identification of a Small-Molecule Inhibitor that Selectively Targets Nav1.8 Sodium Channels, *Mol. Interv.* 7(4): 192-195 (2007); England, Voltage-gated sodium channels: the search for subtype-selective analgesics, *Expert Opin. Investig. Drugs* 17(12): 1849-1864 (2008); Krafte and Bannon, Sodium channels and nociception: recent concepts and therapeutic opportunities, *Curr. Opin. Pharmacol.* 8(1): 50-56 (2008). Navs are the primary mediators of the rapid upstroke of the action potential of many excitable cell types (e.g., neurons, skeletal myocytes, cardiac myocytes), and thus are critical for the initiation of signaling in those cells. Hille and Bertil, *Ion Channels of Excitable Membranes*, 3rd ed. (Sinauer Associates, Inc., Sunderland, MA, 2001). Because of the role Navs play in the initiation and propagation of neuronal signals, antagonists that reduce Nav currents can prevent or reduce neural signaling and Nav channels have long been considered likely targets to reduce pain in conditions where hyper-excitability is observed. Chahine et al., Voltage-gated sodium channels in neurological disorders, *CNS Neurol. Disord. Drug Targets* 7(2): 144-158 (2008). Several clinically useful analgesics have been identified as inhibitors of Nav channels. The local anesthetic drugs such as lidocaine block pain by inhibiting Nav channels, and other compounds, such as carbamazepine, lamotrigine, and tricyclic antidepressants that have proven effective at reducing pain have also been suggested to act by sodium channel inhibition. Soderpalm, Anticonvulsants: aspects of their mechanisms of action, *Eur. J. Pain* 6 (Suppl A): 3-9 (2002); Wang et al., Block of persistent late Na^+ currents by antidepressant sertraline and paroxetine, *J. Membr. Biol.* 222 (2):79-90 (2008).

[0005] The Navs form a subfamily of the voltage-gated ion channel super-family and comprises 9 isoforms designated Nav1.1–Nav1.9. The tissue localizations of the nine isoforms vary greatly. Nav1.4 is the primary sodium channel of skeletal muscle, and Nav1.5 is primary sodium channel of cardiac myocytes. Navs 1.7, 1.8, and 1.9 are primarily localized to the peripheral nervous system, while Navs 1.1, 1.2, 1.3, and 1.6 are neuronal channels found in both the central and peripheral nervous systems. The functional behaviors of the nine isoforms are similar but distinct in the specifics of their voltage-dependent and kinetic behavior. Catterall et al., International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels, *Pharmacol. Rev.* 57(4): 397 (2005).

[0006] Immediately upon their discovery, Nav1.8 channels were identified as likely targets for analgesia. Akopian et al., A tetrodotoxin-resistant voltage-gated sodium channel expressed by

sensory neurons, *Nature* 379(6562): 257-262 (1996). Since then, Nav1.8 has been shown to be the most significant carrier of the sodium current that maintains action potential firing in small DRG neurons. Blair and Bean, Roles of tetrodotoxin (TTX)-sensitive Na^+ current, TTX-resistant Na^+ current, and $Ca2^-$ current in the action potentials of nociceptive sensory neurons, *J. Neurosci.* 22(23): 10277-10290 (2002). Nav1.8 is essential for spontaneous firing in damaged neurons, like those that drive neuropathic pain. Roza et al., The tetrodotoxin-resistant Na^+ channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice, *J. Physiol.* 550(Pt 3): 921-926 (2003); Jarvis et al., A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat, *Proc. Natl. Acad. Sci.* USA 104(20): 8520-8525 (2007); Joshi et al., Involvement of the TTX-resistant sodium channel Nav1.8 in inflammatory and neuropathic, but not post-operative, pain states, *Pain* 123(1-2): 75-82 (2006); Lai et al., Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, Nav1.8, *Pain* 95(1-2): 143-152 (2002); Dong et al., Small interfering RNA-mediated selective knockdown of Na(v)1.8 tetrodotoxin-resistant sodium channel reverses mechanical allodynia in neuropathic rats, *Neuroscience* 146(2): 812-821 (2007); Huang et al., Proteomic profiling of neuromas reveals alterations in protein composition and local protein synthesis in hyper-excitable nerves, *Mol. Pain* 4: 33 (2008); Black et al., Multiple sodium channel isoforms and mitogen-activated protein kinases are present in painful human neuromas, *Ann. Neurol.* 64(6): 644-653 (2008); Coward et al., Immunolocalization of SNS/PN3 and NaN/SNS2 sodium channels in human pain states, *Pain* 85(1-2): 41-50 (2000); Yiangou et al., SNS/PN3 and SNS2/NaN sodium channel-like immunoreactivity in human adult and neonate injured sensory nerves, *FEBS Lett.* 467(2-3): 249-252 (2000); Ruangsri et al., Relationship of axonal voltage-gated sodium channel 1.8 (Nav1.8) mRNA accumulation to sciatic nerve injury-induced painful neuropathy in rats, *J. Biol. Chem.* 286(46): 39836-39847 (2011). The small DRG neurons, where Nav1.8 is expressed, include the nociceptors critical for pain signaling. Nav1.8 is the primary channel that mediates large amplitude action potentials in small neurons of the dorsal root ganglia. Blair and Bean, Roles of tetrodotoxin (TTX)-sensitive Na^+ current, TTX-resistant Na^+ current, and $Ca2^+$ current in the action potentials of nociceptive sensory neurons, *J. Neurosci.* 22(23): 10277-10290 (2002). Nav1.8 is necessary for rapid repetitive action potentials in nociceptors, and for spontaneous activity of damaged neurons. Choi and Waxman, Physiological interactions between Nav1.7 and Nav1.8 sodium channels: a computer simulation study, *J. Neurophysiol.* 106(6): 3173-

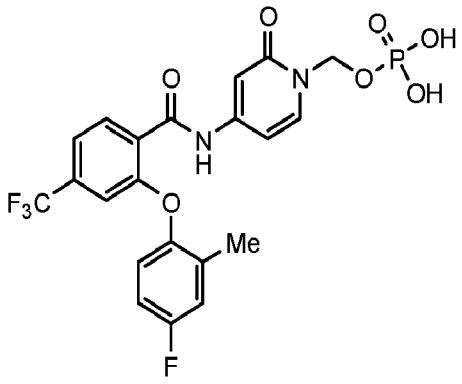
3184 (2011); Renganathan et al., Contribution of Na(v)1.8 sodium channels to action potential electrogenesis in DRG neurons, *J. Neurophysiol.* 86(2): 629-640 (2001); Roza et al., The tetrodotoxin-resistant Na^+ channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice, *J. Physiol.* 550(Pt 3): 921-926 (2003). In depolarized or damaged DRG neurons, Nav1.8 appears to be the primary driver of hyper-excitability. Rush et al., A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons, *Proc. Natl. Acad. Sci. USA* 103(21): 8245-8250 (2006). In some animal pain models, Nav1.8 mRNA expression levels have been shown to increase in the DRG. Sun et al., Reduced conduction failure of the main axon of polymodal nociceptive C-fibres contributes to painful diabetic neuropathy in rats, Brain 135(2): 359-375 (2012); Strickland et al., Changes in the expression of Nav1.7, Nav1.8 and Nav1.9 in a distinct population of dorsal root ganglia innervating the rat knee joint in a model of chronic inflammatory joint pain, *Eur. J. Pain* 12(5): 564-72 (2008); Qiu et al., Increased expression of tetrodotoxin-resistant sodium channels Nav1.8 and Nav1.9 within dorsal root ganglia in a rat model of bone cancer pain, *Neurosci. Lett.* 512(2): 61-6 (2012).

[0007] The primary drawback to some known Nav inhibitors is their poor therapeutic window, and this is likely a consequence of their lack of isoform selectivity. Since Nav1.8 is primarily restricted to the neurons that sense pain, selective Nav1.8 blockers are unlikely to induce the adverse events common to non-selective Nav blockers. Accordingly, there remains a need to develop additional Nav channel modulators, and preferably those that are highly potent and selective for Nav 1.8.

[0008] U.S. Patent Application Publication No. 2014/0213616 A1 discloses a pyridone amide compound useful as an inhibitor of Nav1.8 sodium channels and known by the chemical name 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide. U.S. Patent Application Publication No. 2015/0166589 A1 discloses a prodrug of the foregoing compound, which is known by the chemical name (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate.

SUMMARY

[0009] One embodiment described herein is a pharmaceutical composition comprising a capsule fill of Compound 1:



(I),

and one or more pharmaceutically acceptable suspension agents. Another embodiment is a pharmaceutical composition comprising a capsule fill of Compound 1, or a salt thereof, and one or more pharmaceutically acceptable suspension agents. Another embodiment is a pharmaceutical composition comprising a capsule fill of Compound 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable suspension agents. In one aspect, the Compound 1 is crystalline Form B. In another aspect, the Compound 1 is micronized. In another aspect, the composition comprises about 30% to about 50% of Compound 1 and about 50% to about 70% of one or more pharmaceutically acceptable suspension agents. In another aspect, the composition comprises about 40% of Compound 1 and about 60% of one or more pharmaceutically acceptable suspension agents. In another aspect, the composition comprises about 200–300 mg of Compound 1 and 300–450 mg of the one or more pharmaceutically acceptable suspension agents. In another aspect, the composition comprises about 250 mg of Compound 1 and 375 mg of the one or more pharmaceutically acceptable suspension agents. In another aspect, the pharmaceutically acceptable suspension agent comprises one or more of tocopherol polyethylene glycol succinate (TPGS), lauroyl polyoxyl-32 glycerides, stearoyl polyoxyl-32 glycerides or polyethylene glycol monostearate. In another aspect, the pharmaceutically acceptable suspension agents comprise tocopherol polyethylene glycol succinate (TPGS). In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm. In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$ of about ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm. In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 2.5 μm. In another aspect, the composition comprises: (a) about 30–50% by weight of Compound 1; and (b) about 50–70% by weight of TPGS. In another aspect, the composition comprises: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In another aspect, the composition

comprises a hard capsule dosage form encapsulating the composition. In another aspect, the composition is effective at treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

[0010] Another embodiment described herein is a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof comprising administering an effective amount of any of the compositions described herein.

[0011] Another embodiment described herein is an oral pharmaceutical dosage form comprising a capsule encapsulating a matrix fill comprising: (a) 20–80% by weight of the fill composition of Compound 1; and (b) 20–80% by weight of the fill composition of one or more suspension agents. Another embodiment described herein is an oral pharmaceutical dosage form comprising a capsule encapsulating a matrix fill comprising: (a) 20–80% by weight of the fill composition of Compound 1, or a salt thereof; and (b) 20–80% by weight of the fill composition of one or more suspension agents. Another embodiment described herein is an oral pharmaceutical dosage form comprising a capsule encapsulating a matrix fill comprising: (a) 20–80% by weight of the fill composition of Compound 1, or a pharmaceutically acceptable salt thereof; and (b) 20–80% by weight of the fill composition of one or more suspension agents. In one aspect, the Compound 1 is crystalline Form B. In another aspect, the matrix fill comprises a salt of Compound 1. In another aspect, the Compound 1 is micronized. In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm. In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$ of about ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm. In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$, of about 2.5 μm. In another aspect, the suspension agent comprises one or more of tocopherol polyethylene glycol succinate (TPGS), lauroyl polyoxyl-32 glycerides, stearoyl polyoxyl-32 glycerides, polyethylene glycol monostearate, polyethylene glycols of molecular weight ranging from about 200 to about 8000 (M_N, number average molecular weight), polyvinylpyrrolidone, propylene glycol, or combinations thereof. In another aspect, the dosage form comprises: (a) about 20% to about 50% by weight of Compound 1; and (b) about 50% to about 80% by weight of one or more suspension agents. In another aspect, the dosage form comprises: (a) about 30% to about 40% by weight of Compound 1; and (b) about 60% to about 70% by weight of one or more suspension agents. In another aspect, the dosage form comprises: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of one or more suspension agents. In another aspect, the suspension

agent comprises tocopherol polyethylene glycol succinate (TPGS). In another aspect, the dosage form comprises: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In another aspect, the dosage form comprises about 50 mg to about 2000 mg of Compound 1 in each dosage form. In another aspect, the dosage form comprises about 50 mg, 100 mg, 150 mg, 250 mg, 300 mg, 500 mg, 750 mg, or 1000 mg of Compound 1 in each dosage form. In another aspect, the dosage form comprises about 250 mg to about 300 mg of Compound 1 in each dosage form. In another aspect, the dosage form comprises 250 mg of Compound 1 and 375 mg of TPGS. In another aspect, the capsule is a hydroxypropyl methylcellulose two-piece hard capsule. In another aspect, the dosage form is stable for at least 3 months when stored at a temperature up to 30 °C and a relative humidity up to 65%. In another aspect, about 50% of the dosage form dissolves within about 20 minutes at 37 °C and 75 rpm in a medium of 0.5% polysorbate monolaurate 20 (Tween® 20) in 50 mM sodium acetate buffer (pH 4.5) using a U.S.P. Apparatus 2. In another aspect, the composition is effective at inhibiting voltage gated sodium channel 1.8. In another aspect, the composition is effective at treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

[0012] Another embodiment described herein is the use of any of the dosage forms for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

[0013] Another embodiment described herein is a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof comprising administering an effective amount of any of the dosage forms described herein. In one aspect, the pain comprises one or more of abdominal pain, abnormal gastrointestinal motility pain, acute herpes zoster pain, acute inflammatory pain, acute intermittent pain, acute musculoskeletal pain, acute obstetric pain, acute pain, acute post-operative pain (e.g., bunionectomy pain; abdominoplasty pain; knee pain from a total knee replacement; hip pain from a total hip replacement; pain from a laminectomy; pain from a hernia repair; or hemorrhoid removal pain), acute tendonitis pain, acute visceral pain, adiposis dolorosa pain, amyotrophic lateral sclerosis pain, angina-induced pain, anti-retroviral therapy induced neuralgia, anxiety pain, appendicitis pain, arrhythmia pain, arthritis pain, ataxia pain, back pain, Behçet's disease pain, bipolar disorder pain, bladder and urogenital disease pain, bone pain, brachial plexus avulsion injury pain, breakthrough pain, burn pain, burning mouth syndrome pain, bursitis pain, cancer

chemotherapy induced neuralgia, cancer pain, cardiac arrhythmia pain, cardiac pain, carpal tunnel syndrome pain, central pain, cerebral ischemia, Cesarean-section pain, Charcot-Marie Tooth neuropathic pain, chemotherapy induced neuropathic pain, chest pain, cholecystitis pain, chronic and acute headache pain, chronic and acute neuropathic pain, chronic arthritis, chronic pain, chronic visceral pain, cluster headache pain, cold pain, complex regional pain syndrome, Crohn's disease pain, dental pain (e.g., third molar extraction), depression pain, diabetic neuralgia, diabetic neuropathic pain, diabetic peripheral neuropathic pain, drug therapy induced neuralgia, ectopic proximal and distal discharge pain, endometriosis pain, epilepsy pain, erythromelalgia pain, exercise induced angina pain, exercise induced pain, exercise pain, Fabry's disease pain, femur cancer pain, fibromyalgia pain, general neuralgias, granuloma annulare pain, Guillain-Barre pain, gut pain, Haglund syndrome pain, head pain, headache pain, hereditary sensory neuropathic pain, hernia pain, herpetic neuralgia pain, HIV-associated neuropathic pain, HIV-associated sensory neuropathic pain, hyperactivity bladder pain, hypertension pain, idiopathic pain, idiopathic sensory neuropathic pain, idiopathic small-fiber neuropathic pain, incontinence pain, inflammatory bowel disease pain, inflammatory pain, injury pain, interstitial cystitis (IC) pain, intestinal obstruction pain, intractable pain, irritable bowel syndrome pain, joint pain, labor pain, leprosy pain, lipoidica pain, malignancy pain, mechanical low back pain, migraine pain, Morton's neuroma pain, movement disorder pain, multiple sclerosis (MS) pain, musculoskeletal pain, myofascial pain syndrome pain, myotonia pain, neck pain, necrobiosis pain, nerve avulsion injury pain, nerve entrapment injury pain, neurodegenerative disorder pain, neuroendocrine disorder pain, neuropathic low back pain, neuropathic pain, nociceptive pain, non-malignant chronic bone pain, orofacial pain, osteoarthritis pain, painful bladder syndrome, painful legs, painful moving toes, painful neuromas, palpitations, pancreatic pain, paroxysmal extreme pain, pathological cough pain, pelvic pain, peripheral nerve injury pain, phantom pain, phlebitic pain, post spinal cord injury pain, post-amputation pain, post-herpetic neuralgia, post-mastectomy pain, post-stroke pain, postsurgical pain, premenstrual pain, prostatitis pain, pruritis pain, psychiatric disorder associated pain, pyelonephritis pain, radicular pain, radiculopathy, radiotherapy-induced neuropathic pain, renal colic pain, rheumatoid arthritis pain, sarcoidosis pain, sciatica pain, severe pain, shingles pain, sickle cell anemia pain, sinusitis pain, spinal cord injury pain, spinal stenosis pain, sports injury pain, stress-induced angina pain, stress-induced pain, stroke pain, temporomandibular joint pain, tendonitis pain, tension headache pain, thalamic pain, tinnitus pain, trauma pain, traumatic

brain injury pain, traumatic neuroma, trigeminal autonomic cephalalgia, trigeminal neuralgia, urinary incontinence pain, visceral pain, widespread pain, or other types of pain. In another aspect, the pain is osteoarthritis pain. In another aspect, the pain comprises trigeminal neuralgia. In another aspect, the pain comprises herpetic neuralgia. In another aspect, the pain comprises chronic and acute neuropathic pain. In another aspect, the pain comprises bunionectomy pain. In another aspect, the pain comprises abdominoplasty pain. In another aspect, the pain comprises diabetic peripheral neuropathy. In another aspect, the pain comprises osteoarthritis pain. In another aspect, the pain comprises post-surgical pain from a total knee or total hip replacement or a laminectomy. In another aspect, the pain comprises chronic lower back pain. In another aspect, the pain comprises dental pain. In another aspect, the pain comprises post-surgical pain from a hernia repair or hemorrhoid removal. In another aspect, the pain comprises radiculopathy pain.

[0014] Another embodiment described herein is a method for manufacturing an oral pharmaceutical capsule dosage form comprising: (a) melting one or more suspension agents at a temperature of about 40 °C to about 90 °C; (b) combining Compound 1 with the melted suspension agent of (a) blending the combination, and maintaining the blend at a temperature of about 40 °C to about 90 °C; and (c) encapsulating the blend in 2-piece hard capsules. Another embodiment described herein is a method for manufacturing an oral pharmaceutical capsule dosage form comprising: (a) melting one or more suspension agents at a temperature of about 40 °C to about 90 °C; (b) combining Compound 1, or a salt thereof, with the melted suspension agent of (a) blending the combination, and maintaining the blend at a temperature of about 40 °C to about 90 °C; and (c) encapsulating the blend in 2-piece hard capsules. Another embodiment described herein is a method for manufacturing an oral pharmaceutical capsule dosage form comprising: (a) melting one or more suspension agents at a temperature of about 40 °C to about 90 °C; (b) combining Compound 1, or a pharmaceutically acceptable salt thereof, with the melted suspension agent of (a) blending the combination, and maintaining the blend at a temperature of about 40 °C to about 90 °C; and (c) encapsulating the blend in 2-piece hard capsules. In one aspect, the suspension agent comprises tocopherol polyethylene glycol succinate (TPGS). In another aspect, the temperature of (a) and (b) is about 65 °C. In another aspect, the Compound 1 is crystalline Form B. In another aspect, the dosage form comprises a salt of Compound 1. In another aspect, the Compound 1 is micronized to a median volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm. In another aspect, the Compound 1 is micronized to a median volume

particle size, $D(v,0.5)$ of ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm. In another aspect, the Compound 1 is micronized by jet- or ball-milling.

[0015] Another embodiment described herein is a method for manufacturing an oral pharmaceutical capsule dosage form comprising: (a) melting one or more suspension agents at a temperature of about 40 °C to about 70 °C; (b) combining Compound 1 with the melted suspension agent of (a) blending the combination, and maintaining the blend at a temperature of about 40 °C to about 70 °C; and (c) encapsulating the blend in 2-piece hard capsules. Another embodiment described herein is a method for manufacturing an oral pharmaceutical capsule dosage form comprising: (a) melting one or more suspension agents at a temperature of about 40 °C to about 70 °C; (b) combining Compound 1, or a salt thereof, with the melted suspension agent of (a) blending the combination, and maintaining the blend at a temperature of about 40 °C to about 70 °C; and (c) encapsulating the blend in 2-piece hard capsules. Another embodiment described herein is a method for manufacturing an oral pharmaceutical capsule dosage form comprising: (a) melting one or more suspension agents at a temperature of about 40 °C to about 70 °C; (b) combining Compound 1, or a pharmaceutically acceptable salt thereof, with the melted suspension agent of (a) blending the combination, and maintaining the blend at a temperature of about 40 °C to about 70 °C; and (c) encapsulating the blend in 2-piece hard capsules. In one aspect, the suspension agent comprises tocopherol polyethylene glycol succinate (TPGS). In another aspect, the temperature of (a) and (b) is about 65 °C. In another aspect, the Compound 1 is crystalline Form B. In another aspect, the dosage form comprises a salt of Compound 1. In another aspect, the Compound 1 is micronized to a median volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm. In another aspect, the Compound 1 is micronized to a median volume particle size, $D(v,0.5)$ of ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm. In another aspect, the Compound 1 is micronized by jet- or ball-milling.

[0016] Another embodiment described herein is an oral pharmaceutical capsule dosage form produced by the any of the method described herein. In another aspect, the dosage form comprises: (a) about 40% by weight Compound 1; and (b) about 60% by weight of tocopherol polyethylene glycol succinate (TPGS). In another aspect, the dosage form comprises: (a) about 40% by weight of micronized crystalline Form B of Compound 1; and (b) about 60% by weight of tocopherol polyethylene glycol succinate (TPGS). In another aspect, the dosage form comprises: (a) about 40% by weight of a micronized salt of Compound 1; and (b) about 60% by weight of tocopherol

polyethylene glycol succinate (TPGS). In another aspect, the dosage form comprises about 250 mg to about 300 mg of Compound 1. In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm. In another aspect, the Compound 1 has a median volume particle size, $D(v,0.5)$ of about ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm. In another aspect, the dosage form is effective at treating any type of pain in a subject in need thereof. In another aspect, the pain is osteoarthritis pain. In another aspect, the pain comprises trigeminal neuralgia. In another aspect, the pain comprises herpetic neuralgia. In another aspect, the pain comprises chronic and acute neuropathic pain. In another aspect, the pain comprises bunionectomy pain. In another aspect, the pain comprises abdominoplasty pain. In another aspect, the pain comprises diabetic peripheral neuropathy. In another aspect, the pain comprises osteoarthritis pain. In another aspect, the pain comprises post-surgical pain from a total knee or total hip replacement or a laminectomy. In another aspect, the pain comprises chronic lower back pain. In another aspect, the pain comprises dental pain. In another aspect, the pain comprises post-surgical pain from a hernia repair or hemorrhoid removal. In another aspect, the pain comprises radiculopathy pain.

[0017] Another embodiment described herein is the use of any of the dosage forms described herein for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 shows a scheme for the preparation of capsule dosage forms comprising micronized Compound 1.

[0019] FIG. 2 shows an XRPD spectrum of a sample of jet-milled, crystalline Form B of Compound 1. The salient peaks are shown in Table 2.

[0020] FIG. 3 shows a differential scanning calorimetry (DSC) thermogram for a sample of jet-milled, crystalline Form B of Compound 1.

[0021] FIG. 4 shows an XRPD spectrum of a sample of Compound 1/TPGS capsule fill, prepared as described in Example 4B. The salient peaks are shown in Table 4.

[0022] FIG. 5 shows a differential scanning calorimetry thermogram of a sample of Compound 1/TPGS capsule fill, prepared as described in Example 4B.

[0023] FIG. 6 shows dissolution profiles of hydropropyl methylcellulose capsules containing 250 mg of Compound 1 in 375 mg of TPGS in 0.5% Tween 20, 50 mM sodium acetate, pH 4.5 in a U.S.P. Apparatus 2 at 37 °C and 75 rpm. The capsules had approximately 50% dissolution after about 20 min. The capsules had approximately 90% dissolution after 30 min under the same conditions. The capsules had fully dissolved by about 45 min under the same conditions.

[0024] FIG. 7 shows a scanning electron microscope (SEM) photo of a sample of jet-milled, crystalline Form B of Compound 1.

DETAILED DESCRIPTION

[0025] Described herein are pyridone amide prodrug compositions that inhibit voltage-gated sodium channel modulators. In one embodiment, the pyridone amides are prodrugs that act on voltage-gated sodium channels after cleavage of the prodrug. In another embodiment, the pyridone amides inhibit voltage-gated sodium channel 1.8 (Nav1.8).

[0026] The prodrugs, pharmaceutical compositions, and dosage forms of the compounds described herein are characterized by unexpectedly high aqueous solubility. This solubility facilitates administration of higher doses of the prodrug, resulting in a greater drug load per unit dosage.

[0027] The chemical elements described herein are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed. Additionally, general principles of organic chemistry are described in *Organic Chemistry*, Thomas Sorrell, University Science Books, Sausalito (1999), and *March's Advanced Organic Chemistry*, 5th ed., Ed. Smith and March, John Wiley & Sons, New York (2001), the contents of each of which are hereby incorporated by reference.

[0028] Combinations of substituents described herein are those combinations that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least 3 months.

[0029] The terms "formulation" or "composition" as used herein refers to the drug in combination with pharmaceutically acceptable excipients. These terms include orally administrable formulations as well as formulations administrable by other means.

[0030] The term "treating" refers to administering a therapy in an amount, manner, or mode effective (e.g., a therapeutic effect) to improve a condition, symptom, disorder, or parameter associated with a disorder, or a likelihood thereof.

[0031] The term "prophylaxis" refers to preventing or reducing the progression of a disorder, either to a statistically significant degree or to a degree detectable to one skilled in the art.

[0032] The term "substantially" as used herein means to a great or significant extent, but not completely.

[0033] As used herein, all percentages (%) refer to mass (weight) percent (w/w) unless noted otherwise.

[0034] The term "about" as used herein refers to any values, including both integers and fractional components that are within a variation of up to ±10% of the value modified by the term "about."

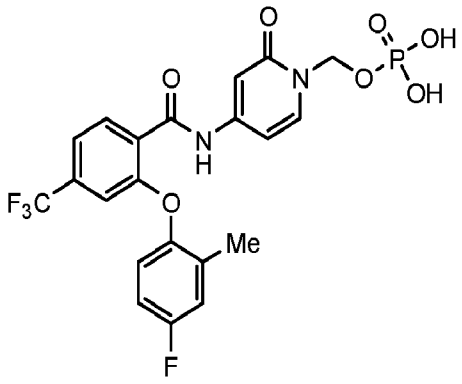
[0035] As used herein, "a" or "an" means one or more unless otherwise specified.

[0036] Terms such as "include," "including," "contain," "containing," "having," and the like mean "comprising."

[0037] The term "or" can be conjunctive or disjunctive.

[0038] As used herein, the term "active pharmaceutical ingredient" or "API" refers to a biologically active compound. Exemplary APIs described herein include a voltage-gated sodium channel inhibitor, e.g., Compound 1 or (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate. In another embodiment, the active pharmaceutical ingredient may also be in the form of pharmaceutically acceptable uncharged or charged molecules, molecular complexes, solvates, or anhydrates thereof, and, if relevant, single isomers, enantiomers, racemic mixtures, or mixtures thereof. In another embodiment, the active pharmaceutical ingredient may be in any of its crystalline, semi-crystalline, amorphous, or polyamorphous forms, or mixtures thereof.

[0039] As used herein, the term "Compound 1" is used interchangeably with "(4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate", which has the following structure:



(Compound 1).

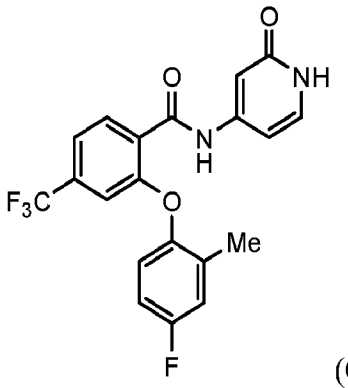
[0040] A synthesis of Compound 1 was described in U.S. Patent No. 9,163,042, which is incorporated herein for such teachings by express reference thereto. The synthesis method is described further in Example 1.

[0041] Compound 1 is a prodrug of its parent compound. Thus, the activity exhibited upon administration of the prodrug is principally due to the presence of the parent compound that results from cleavage of fugitive moieties of the prodrug.

[0042] The term "prodrug" refers to compounds which are drug precursors which, following administration and absorption, release the drug in vivo via some metabolic process. In general, a prodrug possesses less biological activity than its parent drug. A prodrug may also improve the physical properties of the parent drug and/or it may also improve overall drug efficacy, for example through the reduction of toxicity and unwanted effects of a drug by controlling its absorption, blood levels, metabolic distribution and cellular uptake.

[0043] The term "parent compound" or "parent drug" refers to the biologically active entity that is released during a metabolic, catabolic, or chemical reaction following administration of the prodrug. The parent compound may also be the starting material for the preparation of its corresponding prodrug. In one aspect, the parent compound is Compound 2.

[0044] Compound 1 is a prodrug of its parent compound, Compound 2. Compound 2 is used interchangeably with 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide. The synthesis of Compound 2 was described as "Compound 9a" U.S. Patent No. 9,163,042, which is incorporated herein for such teachings by express reference thereto. Compound 2 has the following structure:



(Compound 2).

[0045] The discovery of suitable pharmaceutical compositions and dosage forms for administration of Compound 1 proved to be challenging. The inventors determined that suitable pharmaceutical compositions and dosage forms should deliver a therapeutically effective amount of Compound 1 (and its parent compound, Compound 2) without excessive pill sizes and without exceeding applicable exposure limits for any excipients. The pharmaceutical compositions and dosage forms described herein surprisingly meet all these criteria by delivering therapeutically effective amounts of Compound 1 from easily-swallowed pills and with acceptable amounts of excipients, including suspension agents, such as TPGS.

[0046] Some of the pharmaceutical compositions and dosage forms described herein contain a suspension agent, such as TPGS. The inventors surprisingly found that the use of a suspension agent, such as TPGS, enabled a therapeutically effective amount of Compound 1 to be formulated in pharmaceutical compositions and dosage forms having a relatively small volume, even when the Compound 1 was micronized. The inventors also surprisingly found that the amount or concentration of the suspension agent, such as TPGS, in certain pharmaceutical compositions and dosage forms described herein could be reduced without adversely affecting the bioavailability of Compound 1 (and its parent compound, Compound 2). These surprising results advantageously allow Compound 1 to be administered with a relatively low pill burden and allow the amount of the suspension agent to be reduced.

[0047] Advantageously, certain formulations and dosage forms described herein were found to perform comparably to reference formulations having lower drug loads.

[0048] The foregoing does not constitute a complete characterization of advantages of the pharmaceutical compositions and dosage forms described herein.

[0049] In one embodiment described herein, Compound 1 is the crystalline Form B of Compound 1, or a salt thereof. In another embodiment described herein, Compound 1 is the crystalline Form

B of Compound 1. In another embodiment described herein, Compound 1 is a salt form made from the crystalline Form B of Compound 1.

[0050] Crystalline Form B of Compound 1 is a white to off-white crystalline powder (melting point: 214 °C). The crystal structure of Form B of Compound 1 has been solved and described in U.S. Patent No. 9,163,042, which is incorporated by reference herein for such teachings. Compound 1, Form B has a space group of $P2_1/c$, with the following unit cell dimensions: a = 20.194(9) Å, b = 9.205(4) Å, c = 11.956(5) Å, $\alpha = \gamma = 90°$, β = 95.213(8)°; V = 2213.26 Å^3, Z = 4. The density of Form B calculated from structural data is 1.548 g/cm^3 at 273 K.

[0051] In some embodiments, the present disclosure relates to pharmaceutical compositions and dosage forms comprising Compound 1, or a salt or pharmaceutically acceptable salt thereof, methods involving the administration of same, and methods of manufacturing same. For each embodiment described herein that relates to a pharmaceutical composition or dosage form comprising Compound 1, a method involving the administration of same, or a method of manufacturing same, it will be understood that the disclosure also relates to a corresponding pharmaceutical composition or dosage form comprising Compound 1, or a salt or pharmaceutically acceptable salt thereof, a method involving the administration of same, or a method of manufacturing same. Likewise, for each embodiment described herein that relates to a pharmaceutical composition or dosage form comprising Compound 1, a method involving the administration of same, or a method of manufacturing same, it will be understood that the disclosure also relates to a corresponding pharmaceutical composition or dosage form comprising a salt or pharmaceutically acceptable salt of Compound 1, a method involving the administration of same, or a method of manufacturing same. Where an embodiment refers to the weight or weight percentage of Compound 1, it will be understood that the weight or weight percentage in a corresponding embodiment relating to a salt or pharmaceutically acceptable salt of Compound 1 is based on the equivalent amount of Compound 1, not the amount of the salt or pharmaceutically acceptable salt. In one embodiment, a salt form of Compound 1 is a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" as used herein refers to salts that are suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound described herein or an

inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a voltage-gated sodium channel, e.g., voltage-gated sodium channel 1.8.

[0052] Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describe pharmaceutically acceptable salts in detail in *J. Pharm. Sci.* 66: 1-19 (1977), which is incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. The quaternization of any basic nitrogen-containing groups of the compounds disclosed herein may also provide suitable salts. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0053] The terms "micronized" or "milled" as used herein refers to preparations of Compound 1 that has been subject to comminution to a defined particle size distribution through jet milling, ball milling, or other means known to those of skill in the art.

[0054] In one embodiment, the pharmaceutical compositions or dosage forms described herein comprise solid particles of Compound 1 of a particular size or size distribution. Compound 1 particles may be generated by any particle size reduction or particle growth methodology known to one having ordinary skill the art. Exemplary and non-limiting methods may comprise a "top-down" reduction in particle size including mechanical micronization techniques, wherein a larger particle is crushed, bashed, or ground into a smaller particle through techniques, such as jet milling, ball milling, or high pressure homogenization; or particle engineering techniques such as cryogenic spraying or crystal engineering. In addition, "bottom-up" processing may be used to build a suitable size of particles as described herein using dual solvent/anti-solvent rapid precipitation techniques. *See*, *Handbook of Pharmaceutical Granulation Technology*, CRC Press, 3rd edition, 2010, which is incorporated by reference herein for teachings related to generating pharmaceutical particles. In one aspect described herein, Compound 1 particles of a specified size distribution are produce using a jet milling technique or ball milling.

[0055] In one embodiment, Compound 1 particles are milled or micronized. In one embodiment, the Compound 1 comprises a particle size distribution (d90) of about 0.5 μm to about 100 μm, including all integers and fractions within the specified range. In another embodiment, the Compound 1 particles have median volume particle size distributions $D(v,0.5)$ ranging from about 0.5 μm to about 100 μm, including all integers and fractions within the specified range. In one aspect, the solid particles of Compound 1 comprise median volume particle size distributions $D(v,0.5)$ of about 1 μm to about 50 μm, including all integers and fractions within the specified range. In one aspect, the solid particles of Compound 1 comprise median volume particle size distributions $D(v,0.5)$ of about 1 μm to about 20 μm, including all integers and fractions within the specified range. In one aspect, the solid particles of Compound 1 comprise median volume particle size distributions $D(v,0.5)$ of about 1 μm to about 10 μm, including all integers and fractions within the specified range. In one aspect, the solid particles of Compound 1 comprise median volume particle size distributions $D(v,0.5)$ of about 1 μm to about 5 μm, including all integers and fractions within the specified range. In one aspect, the solid particles of Compound 1 comprise median volume particle size distributions $D(v,0.5)$ of about 1 μm to about 3 μm, including all integers and fractions within the specified range.

[0056] In another embodiment, the solid particles of Compound 1 comprise median volume particle size distributions $D(v,0.5)$ of about 0.5 μm, about 1.0 μm, about 1.5 μm, about 2.0 μm,

about 2.5 μm, about 3.0 μm, about 3.5 μm, about 4.0 μm, about 4.5 μm, about 5 μm, about 5.5 μm, about 6.0 μm, about 6.5 μm, about 7.0 μm, about 7.5 μm, about 8.0 μm, about 8.5 μm, about 9.0 μm, about 9.5 μm, or about 10 μm.

[0057] In another embodiment, the solid particles of Compound 1 have a median volume particle size distribution $D(v,0.5)$ of about 0.5 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of about 1 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of about 2 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of about 2.5 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of about 3.0 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of about 4.0 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of < 5.0 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of < 10.0 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of < 20 μm. In one aspect, the solid particles of Compound 1 have a particle size $D(v,0.5)$ of about 2–3 μm.

[0058] In another embodiment, Compound 1 is micronized to a median volume particle size, $D(v,0.5)$, of about 1–20 μm, 1–10 μm, 1–5 μm, 1–3 μm, 2–5 μm, 3–5 μm, or 2–3 μm.

[0059] In another embodiment, Compound 1 is micronized to a median volume particle size, $D(v,0.5)$, of ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm. In one aspect, crystalline Form B of Compound 1 is micronized to a median volume particle size, $D(v,0.5)$, of about 2–3 μm.

[0060] In another embodiment, the solid particles of Compound 1 have a $D(v,0.5)$ of about 2 μm to about 3 μm, a surface area weighed particle size, SMD or $D[3,2]$, of about 1.1 μm to about 1.6 μm, and a volume weighed particle size, VMD or $D[4,3]$ of about 1.9 μm to about 2.5 μm.

[0061] In another embodiment, the solid Compound 1 particles have a particle size distribution with a d90 of less than or equal to about 5 μm. In one aspect, the particle size distribution of solid particles of Compound 1 have a d90 of less than or equal to about 10 μm, about 9 μm, about 8 μm, about 7 μm, about 6 μm, about 5 μm, about 4 μm, about 3 μm, about 2 μm, or about 1 μm. In one aspect, the solid particles of Compound 1 have a particle size distribution with a d90 of less than or equal to about 10 μm (d90 $\leq$10 μm). In one aspect, the solid particles of Compound 1 have a particle size distribution with a d90 of less than or equal to about 5 μm (d90 $\leq$5 μm). In one aspect, the solid particles of Compound 1 have a particle size distribution with a d90 of less than or equal

to about 4 μm (d90 ≤ 4 μm). In one aspect, the solid particles of Compound 1 have a particle size distribution with a d90 of less than or equal to about 3 μm (d90 ≤ 3 μm). In one aspect, the solid particles of Compound 1 have a particle size distribution with a d90 of less than or equal to about 2 μm (d90 ≤ 2 μm).

[0062] In another embodiment, the solid particles of Compound 1 comprise multiple distributions of particle sizes. In one aspect, the solid particles of Compound 1 may comprise a plurality of independently combined mean particle size distributions, wherein each independent mean particle size distribution ranges from about 1 μm to about 200 μm, including all integers and fractions within the specified range. In another aspect, the plurality of mean particle size distributions can comprise a mean particle size distribution of about 1 μm to about 10 μm. In another aspect, the plurality of mean particle size distributions can comprise combinations of independent mean particle size distributions, wherein each independently combined mean particle size distribution is about 2 μm, about 5 μm, about 10 μm, about 15 μm, about 20 μm; about 50 μm, about 100 μm, or about 200 μm. In another aspect, the solid particles of Compound 1 comprise a combination of independently combined mean particle size distributions of about 1 μm to about 100 μm in a single dosage form. Any of the foregoing particle size distributions may be combined to provide the desired controlled release profile.

[0063] The foregoing sizes of Compound 1 particles may be determined using standard techniques known to one of ordinary skill in the art. The exemplary techniques that can be used for measuring the size of Compound 1 particles may include laser diffraction analysis, light scattering (e.g., dynamic light scattering), microscopic particle image analysis, elutriation, or aerosol mass spectrometry. The sample of Compound 1 particles may be measured as a dry sample or a wet sample. Any commercially available instrument for measuring particle sizes may be used, including instruments from Sympatec; Cilas; Brookhaven Instruments Corporation; Malvern Instruments; Horiba Scientific; or Wyatt following the recommended operating procedures according to the manufacturer's instructions.

[0064] The measured particle sizes using the techniques described herein may be expressed as a derived diameter with a normal distribution or non-normal distribution with a mean, median (e.g., mass median diameter), and mode of particle diameter sizes. The particle size distribution may be expressed as a diameter number distribution, a surface area distribution, or a particle volume distribution. The mean of the particle size distribution may be calculated and expressed in various

ways, such as the volume mean diameter (D[4,3] or d_{43}), mean surface area diameter (D[3,2] or d_{32}) or the mean number particle diameter (D[1,0] or d_{10}). Because the particle size distribution values vary depending on the measurement methodology and how the distribution is expressed, the comparison of different mean particle size distributions must be calculated by the same methodology in order to yield an accurate comparison. For example, a sample with a measured and calculated volume mean diameter must be compared with a second sample having a measured and calculated volume mean diameter, ideally measured using the same measuring instrument under the same conditions. Thus, the specific particle size distributions described herein are not intended to be limited to any one type of method for measuring or calculating a particle size distribution (e.g., a diameter number distribution, a surface area distribution, or a particle volume distribution), but rather indicate particle size values and distributions thereof for each method of measuring particle sizes described herein. As used herein, Dv50 or D(v,0.5) refers to the median (50%) particle size distribution for a volume distribution. For a particular sample, 50% of the particles are larger than the D(v,0.5) value and 50% are smaller.

[0065] Another embodiment described herein is a method for manufacturing particles of Compound 1 of defined sizes using jet milling, ball milling, or other techniques for comminution. In one aspect, the particles are of a similar size distribution. In another aspect, the Compound 1 particles comprise varied size distributions. In another aspect, the Compound 1 particles comprise several size distributions. In another aspect, the Compound 1 particles comprise a mixture of smaller and larger size distributions. Without being bound to any theory, smaller particles are generally solubilized and released more rapidly than larger particles. The release rate can be adjusted to achieve a specific therapeutic window over a defined period and produce controlled release, delayed release, or extended release compositions by combining multiple Compound 1 particle sizes or size distributions.

[0066] Another embodiment described herein is a pharmaceutical dosage form comprising Compound 1 or crystalline form thereof.

[0067] One embodiment described herein is a pharmaceutical composition comprising a crystalline form of Compound 1 or a salt or crystalline form thereof. One embodiment described herein is a pharmaceutical composition comprising a crystalline form of Compound 1 or a crystalline form thereof. Another embodiment described herein is a pharmaceutical composition comprising a crystalline form of Compound 1 or a salt or crystalline form thereof and one or more

pharmaceutically acceptable excipients. Another embodiment described herein is a pharmaceutical composition comprising a crystalline form of Compound 1 or a crystalline form thereof and one or more pharmaceutically acceptable excipients. In one embodiment, the crystalline form of Compound 1 is crystalline Form B. In another embodiment, the pharmaceutical composition comprises micronized or milled particles of crystalline Form B of Compound 1. In one aspect, crystalline Form B of Compound 1 is micronized to a median volume particle size, $D(v,0.5)$, of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm. In another aspect, crystalline Form B of Compound 1 is micronized to a median volume particle size, $D(v,0.5)$, of ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2 μm. In another aspect, crystalline Form B of Compound 1 is micronized to a median volume particle size, $D(v,0.5)$ of about 2–3 μm. In one aspect, the composition comprises about 20% to about 80% of Compound 1, or a salt or crystalline form thereof, and about 20% to about 80% of the one or more pharmaceutically acceptable excipients. In one aspect, the composition comprises about 20% to about 80% of Compound 1, or a crystalline form thereof, and about 20% to about 80% of the one or more pharmaceutically acceptable excipients. In another aspect, the pharmaceutical composition comprises about 50 mg to about 2000 mg, including each integer within the specified range, of Compound 1 or a salt or crystalline form thereof. In another aspect, the pharmaceutical composition comprises about 50 mg to about 2000 mg, including each integer within the specified range, of Compound 1 or a crystalline form thereof. In one aspect, the pharmaceutical composition comprises an oral dosage form, including but not limited to a hard or soft capsule.

[0068] Another embodiment described herein is an oral pharmaceutical composition comprising: (a) one or more active pharmaceutical ingredients comprising micronized crystalline Form B of Compound 1; and (b) one or more suspension agents. In one aspect, the suspension agent comprises one or more of tocopherol polyethylene glycol succinate (TPGS), polyethylene glycols of molecular weight ranging from about 200 to about 8000 (M_N, number average molecular weight), polyvinylpyrrolidone, propylene glycol, glycerol, or combinations thereof. In one aspect, the suspension agent comprises tocopherol polyethylene glycol succinate (TPGS).

[0069] In one embodiment described herein, the oral pharmaceutical composition comprises the formulation of Table 1.

Table 1. Exemplary Oral Dosage Form of Compound 1		
Component	**Exemplary Species**	**% mass**
API	Compound 1 (e.g., micronized, Form B)	20–60
Suspension agent(s)	TPGS, Gelucire® 44/14, PEGs	40–80
Optional Excipients	Various	0–10%

[0070] In another embodiment described herein, the oral pharmaceutical composition comprises the formulation of Table 1A.

Table 1A. Exemplary Oral Dosage Form of Compound 1		
Component	**Exemplary Species**	**% mass**
API	Compound 1 (e.g., micronized, Form B)	20–60
Suspension agent(s)	TPGS, Gelucire® 44/14, PEGs	40–80
Optional Excipients	Various	1–10%

[0071] Another embodiment described herein is an oral pharmaceutical composition comprising: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of one or more suspension agents. In one aspect, the composition comprises (a) about 15% to about 40% by weight of Compound 1; and (b) about 40% to about 80% by weight of one or more suspension agents. In one aspect, the composition comprises (a) about 40% by weight of Compound 1; and (b) about 60% by weight of one or more suspension agents. In one aspect the suspension agent comprises one or more of tocopherol polyethylene glycol succinate (TPGS), lauroyl polyoxyl-32 glycerides, stearoyl polyoxyl-32 glycerides, or polyethylene glycol monostearate. In one aspect the suspension agent is tocopherol polyethylene glycol succinate (TPGS). In another aspect the suspension agent is lauroyl polyoxyl-32 glycerides (Gelucire® 44/14). In another aspect the suspension agent is polyethylene glycol monostearate (Gelucire® 48/16). In another aspect the suspension agent is stearoyl polyoxyl-32 glycerides (Gelucire® 50/13). In one aspect, the Compound 1 comprises micronized crystalline Form B of Compound 1.

[0072] Another embodiment described herein is an oral pharmaceutical composition consisting essentially of: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of one or more suspension agents. In one aspect, the composition consists essentially of (a) about 15% to about 40% by weight of Compound 1; and (b) about 40% to about 80% by weight of one or more suspension agents. In one aspect, the composition consists

essentially of (a) about 40% by weight of Compound 1; and (b) about 60% by weight of one or more suspension agents. In one aspect the suspension agent is one or more of tocopherol polyethylene glycol succinate (TPGS), lauroyl polyoxyl-32 glycerides, stearoyl polyoxyl-32 glycerides, or polyethylene glycol monostearate. In one aspect the suspension agent is tocopherol polyethylene glycol succinate (TPGS). In another aspect the suspension agent is lauroyl polyoxyl-32 glycerides (Gelucire® 44/14). In another aspect the suspension agent is polyethylene glycol monostearate (Gelucire® 48/16). In another aspect the suspension agent is stearoyl polyoxyl-32 glycerides (Gelucire® 50/13). In one aspect, the Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0073] Another embodiment described herein is an oral pharmaceutical composition consisting of: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of one or more suspension agents. In one aspect, the composition consists of (a) about 15% to about 40% by weight of Compound 1; and (b) about 40% to about 80% by weight of one or more suspension agents. In one aspect, the composition consists of (a) about 40% by weight of Compound 1; and (b) about 60% by weight of one or more suspension agents. In one aspect the suspension agent is one or more of tocopherol polyethylene glycol succinate (TPGS), lauroyl polyoxyl-32 glycerides, stearoyl polyoxyl-32 glycerides, or polyethylene glycol monostearate. In one aspect the suspension agent is tocopherol polyethylene glycol succinate (TPGS). In another aspect the suspension agent is lauroyl polyoxyl-32 glycerides (Gelucire® 44/14). In another aspect the suspension agent is polyethylene glycol monostearate (Gelucire® 48/16). In another aspect the suspension agent is stearoyl polyoxyl-32 glycerides (Gelucire® 50/13). In one aspect, the Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0074] In another aspect, the composition comprises about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of Compound 1. In another aspect, the composition comprises about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by

weight of Compound 1, and at least about 20% by weight of one or more suspension agents. In one aspect, the Compound 1 comprises micronized crystalline Form B of Compound 1. In another aspect, the composition comprises any of the foregoing concentrations of a salt of Compound 1. In another aspect, the suspension agent is TPGS.

[0075] In another aspect, the composition comprises about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of one or more suspension agents. In another aspect, the composition comprises about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% of one or more suspension agents, and at least about 20% by weight of Compound 1. In one aspect, the Compound 1 comprises micronized crystalline Form B of Compound 1. In another aspect, the suspension agent is TPGS. In another aspect, the composition comprises at least 20% by weight of a salt of Compound 1.

[0076] In some aspects, the composition comprises about 25% by weight of Compound 1 and about 75% by weight of one or more suspension agents. In some aspects, the composition comprises about 27.5% by weight of Compound 1 and about 72.5% by weight of one or more suspension agents. In some aspects, the composition comprises about 30% by weight of Compound 1 and about 70% by weight of one or more suspension agents. In some aspects, the composition comprises about 32.5% by weight of Compound 1 and about 68.5% by weight of one or more suspension agents. In some aspects, the composition comprises about 35% by weight of Compound 1 and about 65% by weight of one or more suspension agents. In some aspects, the composition comprises 37.5% by weight of Compound 1 and about 62.5% by weight of one or more suspension agents. In some aspects, the composition comprises 40% by weight of Compound 1 and about 60% by weight of one or more suspension agents. In some aspects, the composition comprises about 42.5% by weight of Compound 1 and about 57.5% by weight one or more suspension agents. In some aspects, the composition comprises about 45% by weight of Compound 1 and about 55% by weight of one or more suspension agents. In some aspects, the composition comprises about 47.5% by weight of Compound 1 and about 52.5% by weight of one

or more suspension agents. In some aspects, the composition comprises about 50% by weight of Compound 1 and about 50% by weight of one or more suspension agents. In another aspect, the composition comprises about 52.5% by weight of Compound 1 and about 47.5% by weight of one or more suspension agents. In another aspect, the composition comprises about 55% by weight of Compound 1 and about 45% by weight of one or more suspension agents. In one aspect, the Compound 1 comprises micronized crystalline Form B of Compound 1. In another aspect, the suspension agent is TPGS. In another aspect, the composition comprises any of the foregoing concentrations of a salt of Compound 1.

[0077] In another aspect, the composition consists essentially of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of Compound 1, and one or more suspension agents. In another aspect, the composition consists essentially of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of Compound 1, and at least about 20% by weight of one or more suspension agents. In one aspect, the Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the composition contains a salt of Compound 1 in any of the foregoing concentrations provided for Compound 1. In another aspect, the suspension agent is TPGS.

[0078] In another aspect, the composition consists of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of Compound 1, and one or more suspension agents. In another aspect, the composition consists of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of Compound 1, and at least about 20% by weight of one or more suspension agents. In one aspect, the Compound 1 is micronized crystalline Form B

of Compound 1. In another aspect, the composition contains a salt of Compound 1 in any of the foregoing concentrations provided for Compound 1. In another aspect, the suspension agent is TPGS.

[0079] In another aspect, the composition consists essentially of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of one or more suspension agents; and Compound 1. In another aspect, the composition consists essentially of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% of one or more suspension agents, and at least about 20% by weight of Compound 1. In one aspect, the Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the suspension agent is TPGS. In another aspect, the composition contains a salt of Compound 1.

[0080] In another aspect, the composition consists of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% by weight of one or more suspension agents; and Compound 1. In another aspect, the composition consists of about 20%, about 22.5%, about 25%, about 27.5%, about 30%, about 32.5%, about 35%, about 37.5%, about 40%, about 42.5%, about 45%, about 47.5%, about 50%, about 52.5%, about 55%, about 57.5%, about 60%, about 62.5%, about 65%, about 67.5%, about 70%, about 72.5%, about 75%, about 77.5%, or about 80% of one or more suspension agents, and at least about 20% by weight of Compound 1. In one aspect, the Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the suspension agent is TPGS. In another aspect, the composition contains a salt of Compound 1.

[0081] Another embodiment described herein is an oral pharmaceutical composition comprising: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the composition comprises (a) about 15% to about 40% by weight of Compound 1; and (b) about 40% to about 80% by weight

of TPGS. In one aspect, the composition comprises (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In one aspect, the Compound 1 comprises micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0082] Another embodiment described herein is an oral pharmaceutical composition consisting essentially of: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the composition consists essentially of (a) about 15% to about 40% by weight of Compound 1; and (b) about 40% to about 80% by weight of TPGS. In one aspect, the composition consists essentially of (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In one aspect, the Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0083] Another embodiment described herein is an oral pharmaceutical composition consisting of: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the composition consists of (a) about 15% to about 40% by weight of Compound 1; and (b) about 40% to about 80% by weight of TPGS. In one aspect, the composition consists of (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In one aspect, the Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0084] Another embodiment described herein is an oral pharmaceutical composition comprising: (a) about 20% to about 80% by weight of Compound 1, or a salt thereof; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the composition comprises (a) about 15% to about 40% by weight of Compound 1, or a salt thereof; and (b) about 40% to about 80% by weight of TPGS. In one aspect, the composition comprises (a) about 40% by weight of Compound 1, or a salt thereof; and (b) about 60% by weight of TPGS. In one aspect, the crystal form of Compound 1 comprises micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0085] Another embodiment described herein is an oral pharmaceutical composition consisting essentially of: (a) about 20% to about 80% by weight of Compound 1, or a salt thereof; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one

aspect, the composition consists essentially of (a) about 15% to about 40% by weight of Compound 1, or a salt thereof; and (b) about 40% to about 80% by weight of TPGS. In one aspect, the composition consists essentially of (a) about 40% by weight of Compound 1, or a salt thereof; and (b) about 60% by weight of TPGS. In one aspect, the crystal form of Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0086] Another embodiment described herein is an oral pharmaceutical composition consisting of: (a) about 20% to about 80% by weight of Compound 1, or a salt thereof; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the composition consists of (a) about 15% to about 40% by weight of Compound 1, or a salt thereof; and (b) about 40% to about 80% by weight of TPGS. In one aspect, the composition consists of (a) about 40% by weight of Compound 1, or a salt thereof; and (b) about 60% by weight of TPGS. In one aspect, the crystal form of Compound 1 is micronized crystalline Form B of Compound 1. In another aspect, the pharmaceutical composition comprises a salt of Compound 1.

[0087] Another embodiment described herein is an oral pharmaceutical composition comprising: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In one aspect, the composition comprises about 50 mg to about 2000 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 50 mg, 100 mg, 150 mg, 250 mg, 300 mg, 500 mg, 750 mg, 1000 mg, 1250 mg, 1500 mg, or 2000 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 250 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 300 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 500 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 750 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 1000 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 1500 mg of Compound 1 in each dosage form. In another aspect, the composition comprises about 2000 mg of Compound 1 in each dosage form. In another aspect, the composition is effective at inhibiting a voltage gated sodium channel. In another aspect, the composition is effective at inhibiting voltage gated sodium channel 1.8. In another aspect, the composition comprises a hard capsule dosage form. In another aspect, the composition is effective at treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

[0088] Another embodiment is a soft capsule dosage form comprising Compound 1. In one aspect, the soft capsule dosage from comprises a flowable matrix fill encapsulated within a film-forming polymer based shell. Often the film-forming polymer is gelatin. The matrix can comprise a liquid, semisolid, or emulsion fill. In one aspect, the fill is a hydrophilic or aqueous fill. In another aspect, the fill is a hydrophobic fill. In another aspect, the fill is an emulsion.

[0089] In one embodiment, the matrix comprises one or more hydrophilic solvents or suspension agents. The matrix can be polyvinylpyrrolidone, polyethylene glycols of molecular weight ranging from about 200 to about 8000 (M_N, number average molecular weight), or combinations thereof. In one embodiment, the matrix comprises polyvinylpyrrolidone K30 (e.g., Povidone K30). In another embodiment, the matrix comprises polyethylene glycol and polyvinylpyrrolidone.

[0090] In another embodiment, the lipid or lipophilic liquid vehicle comprises one or more oils, mono/diglycerides, polyoxyl hydrogenated castor oils, polyvinylpyrrolidones, or combinations thereof. In another embodiment, the lipid or lipophilic liquid vehicle comprises an oil. In another embodiment, the lipid or lipophilic vehicle comprises mono/diglycerides, polyoxyl hydrogenated castor oils, polyvinylpyrrolidones, or combinations thereof.

[0091] Exemplary lipid or lipophilic vehicles comprise mineral oil; light mineral oil; natural oils (e.g., vegetable, corn, canola, sunflower, soybean, olive, coconut, cocoa, peanut, almond, cottonseed, persic, sesame, squalene, castor, cod liver) hydrogenated vegetable oil; partially hydrogenated oils; beeswax; polyethoxylated beeswax; paraffin; normal waxes; medium chain medium chain monoglycerides, diglycerides and triglycerides; higher aliphatic alcohols; higher aliphatic acids; long chain fatty acids; saturated or unsaturated fatty acids; hydrogenated fatty acids; fatty acid glycerides; polyoxyethylated oleic glycerides; monoglycerides and diglycerides; mono-, bi- or tri-substituted glycerides; glycerol mono-oleate esters; glycerol mono-caprate; glyceryl monocaprylate; propylene glycol dicaprylate; propylene glycol monolaurate; glyceryl palmitostearate; glyceryl behenate; diethyleneglycol palmitostearate; polyethyleneglycol stearate; polyoxyethyleneglycol palmitostearate; glyceryl mono palmitostearate; cetyl palmitate; polyethyleneglycol palmitostearate; dimethylpolysiloxane; mono- or di-glyceryl behenate; lauroyl polyoxyl-32 glycerides; fatty alcohols associated with polyethoxylate fatty alcohols; cetyl alcohol; octyl dodecanol; myristyl alcohol; isopropyl myristate, isopropyl palmitate, stearic acid, or stearyl alcohol, inter alia, or combinations thereof. In one embodiment, the liquid matrix comprises solid particles of Form B of Compound 1 suspended in a lipid or lipophilic vehicle of vegetable oil, fatty

acid, fatty acid ester, or a combination thereof. In one embodiment, the lipid or lipophilic vehicle is a liquid at room temperature (e.g., 25 °C) or physiological temperature (e.g., 37 °C). In one embodiment, the lipid or lipophilic vehicle is soybean oil. In another embodiment, the lipid or lipophilic vehicle comprises medium chain monoglycerides and diglycerides.

[0092] In one embodiment, the matrix comprises a solvent or solubility enhancing agent. Exemplary solvents or solubility enhancing agents useful for the matrix fills described herein include Capmul® MCM, Cremophor® RH 40, Captex® 355, Croscarmellose, Crospovidone, Crospovidone CL, Crospovidone CL-F, Crospovidone CL-M, Imwitor® 742, Kollidon® CL, Kollidon® CL-F, Kollidon® CL-M, Labrafac™, Lipophile WL 1349, Labrafil® M2125CS, Labrasol®, Lutrol® F 68, Maisine™ 35-1, mannitol, Miglyol® 812, Pearlitol® Flash, Peceol®, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 3350, Plurol® Oleique CC 497, Povidone K 17, Povidone K 30, propylene glycol, or combinations thereof. In one embodiment, the lipid or lipophilic vehicle comprises medium chain mono- and diglycerides (e.g., Capmul® MCM) and polyoxyl 40 hydrogenated castor oil (e.g., macrogolglycerol hydroxystearate; Cremophor® RH 40).

[0093] In another embodiment, the matrix fill comprises a release regulator such as a fatty acid salt, fatty acid ester, or fatty acid polyoxyethylene derivative. The release regulator can also be a surfactant having a hydrophilic/lipophilic balance (HLB) value between about 2 and about 40. The HLB characteristic of surfactants can be determined in accordance with "*Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*," Fourth Edition, pp. 371-373, A. Martin, Ed., Lippincott Williams & Wilkins, Philadelphia (1993), which is incorporated by reference herein for such teachings.

[0094] In another embodiment, the matrix comprises emulsifying or solubilizing agents such as acacia, cholesterol, diethanolamine, glyceryl monostearate, lanolin alcohols, lecithin, mono- and di-glycerides, monoethanolamines, oleic acids, oleyl alcohols, poloxamer, polyoxyethylene 50 stearate, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol diacetate, propylene glycol monostearate, sodium lauryl sulfate, sodium stearate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, stearic acid, trolamine, emulsifying wax, or combinations thereof.

[0095] In another embodiment, the matrix comprises a neutralizing agent. Without being bound to any theory, the neutralizing agent is thought to stabilize the Form B of Compound 1 in the matrix fill by preventing hydrolysis. In addition, without being bound by any theory, the neutralizing agent may stabilize soft capsule shells comprising enteric polymers such as acrylate methacrylate by forming salts with the methylacrylate moieties from the capsule shell. In one aspect, the neutralizing agent comprises an organic acid, ester, or salt. In another aspect, the neutralizing agent comprises at least one of lactate, fumarate, caprylate, caprate, oleate, maleate, succinate, tartrate, citrate, glutamate, gluconate, esters or salts thereof, or combinations thereof. In one aspect, the neutralizing agent is lactic acid.

[0096] In another embodiment, the matrix includes a hydrophilic internal phase and a lipid or lipophilic external phase. The hydrophilic internal phase can comprise polypropylene glycol or polyethylene glycol of molecular weight ranging from about 200 to about 8000 (M_N, number average molecular weight). In another embodiment, the internal phase comprises hydroalcoholic solutions of cellulose derivatives, polyacrylates, polyvinyl polymers, or combinations thereof. In one embodiment, the internal phase comprises polymers such as methylcellulose, hydroxypropyl methylcellulose, polymethylmethacrylate, or polyvinylpyrrolidone (PVP). In one embodiment, the internal phase of the matrix state is "fluid" or "structured." A "fluid" internal phase, as used herein, means a completely flowable liquid whose globules can aggregate to make a larger globule. A "structured" internal phase, as used herein, means a solid, semisolid, or a gel whose shape is relatively stable and does not usually aggregate to form a large globule. A structured internal phase can provide controlled drug release and stabilize the physical state of the matrix. Without being bound to any theory, the structured nature of the matrix impedes solvation or diffusion of the Form B of Compound 1 out of the matrix. In another embodiment, the external phase comprises a vegetable oil, hydrogenated vegetable oil, fatty acid, fatty acid ester, wax, or a combination thereof. In another embodiment, Form B of Compound 1 is dispersed in the internal phase as a suspension form.

[0097] In another embodiment, the matrix fill is an emulsion type, where the Form B of Compound 1 is distributed in one or both of the external (lipophilic) and internal (hydrophilic) phases. The external phase of the emulsion matrix fill comprises lipid or lipophilic vehicles similar to those described herein. The Form B of Compound 1 can be dispersed in the internal phase as a solution or as a suspension. For example, one portion of the Form B of Compound 1 in the form of a

powder is incorporated in the internal phase, while another portion is dispersed in the external phase as solid particles. An emulsion-type matrix may comprise a surfactant or combination of surfactants having HLB values ranging from about 2 to about 40, including all integers within the specified range. In one aspect, the HLB range comprises from about 8 to about 20, including all integers within the specified range.

[0098] The soft capsule matrix fill is flowable such that it can be encapsulated using a rotary die encapsulation machine. In one embodiment, the matrix components are heated to a temperature in the range of from about 25 °C to about 75 °C. In another embodiment, the matrix components are heated to a temperature in the range of from about 50 °C to about 70 °C.

[0099] In one aspect, soft capsules are made using a rotary die apparatus as described in U.S. Patent Nos. 5,459,983; 5,146,730; and 6,482,516, each of which are incorporated by reference herein for such teachings.

[00100] Another embodiment described herein includes a process of manufacturing soft capsules comprising any of the pharmaceutical compositions as described herein. The process includes preparing a gel mass composition comprising a film-forming, water-soluble polymer, an appropriate plasticizer, and solvent; casting the gel mass into films or ribbons using heat-controlled drums or surfaces; and manufacturing a soft capsule comprising a matrix fill using rotary die technology. The thickness of the films or ribbons that form the soft capsule shell is from about 0.010 inches (≈0.254 mm) to about 0.050 inches (≈1.27 mm), including all integers within the specified range.

[00101] Another embodiment described herein is an oral pharmaceutical dosage form comprising a capsule encapsulating a matrix fill comprising: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of one or more suspension agents. Another embodiment described herein is an oral pharmaceutical dosage form comprising a capsule encapsulating a matrix fill comprising: (a) about 20% to about 50% by weight of Compound 1; and (b) about 50% to about 80% by weight of one or more suspension agents. In one aspect, the dosage form comprises: (a) about 30% to about 40% by weight of Compound 1; and (b) about 60% to about 70% by weight of one or more suspension agents. In another aspect, the dosage form comprises: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of one or more suspension agents. In another aspect, the dosage form consists essentially of: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of one or

more suspension agents. In another aspect, the dosage form consists essentially of: (a) about 20% to about 50% by weight of Compound 1; and (b) about 50% to about 80% by weight of one or more suspension agents. In one aspect, the dosage form consists essentially of: (a) about 30% to about 40% by weight of Compound 1; and (b) about 60% to about 70% by weight of one or more suspension agents. In another aspect, the dosage form consists essentially of: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of one or more suspension agents. In another aspect, the dosage form consists of: (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of one or more suspension agents. In another aspect, the dosage form consists of: (a) about 20% to about 50% by weight of Compound 1; and (b) about 50% to about 80% by weight of one or more suspension agents. In one aspect, the dosage form consists of: (a) about 30% to about 40% by weight of Compound 1; and (b) about 60% to about 70% by weight of one or more suspension agents. In another aspect, the dosage form consists of: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of one or more suspension agents. In another aspect, the suspension agent comprises tocopherol polyethylene glycol succinate (TPGS). In another aspect, the dosage form comprises (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In another aspect, the dosage form comprises: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In another aspect, the dosage form consists essentially of (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In another aspect, the dosage form consists essentially of: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In another aspect, the dosage form consists of (a) about 20% to about 80% by weight of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In another aspect, the dosage form consists of: (a) about 40% by weight of Compound 1; and (b) about 60% by weight of TPGS. In another aspect, the dosage form comprises about 50 mg to about 2000 mg of Compound 1. In another aspect, the dosage form comprises about 75 mg to about 3000 mg of TPGS. In another aspect, the capsule is a hydroxypropyl methylcellulose two-piece hard capsule. In another aspect, the dosage form comprises a salt of Compound 1. In another aspect, the dosage form comprises crystalline Form B of Compound 1. In another aspect, the dosage form comprises micronized crystalline Form B of Compound 1. In one aspect, crystalline Form B of Compound 1 is micronized to a median

volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm. In another aspect, crystalline Form B of Compound 1 is micronized to a median volume particle size, $D(v,0.5)$ of ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm. In another aspect, crystalline Form B of Compound 1 is micronized to a median volume particle size, $D(v,0.5)$ of about 2–3 μm. In another aspect, the dosage form comprises about 100 mg of Compound 1. In another aspect, the dosage form comprises about 250 mg of Compound 1. In another aspect, the dosage form comprises about 300 mg of Compound 1. In another aspect, the dosage form comprises about 500 mg of Compound 1. In another aspect, the dosage form comprises about 750 mg of Compound 1. In another aspect, the dosage form comprises about 1000 mg of Compound 1. In another aspect, the dosage form comprises about 1500 mg of Compound 1. In another aspect, the dosage form comprises about 2000 mg of Compound 1. In another aspect, the dosage form is stable for at least 3 months when stored at a temperature up to 30 °C and a relative humidity up to 65%. In another aspect, about 50% of the dosage form dissolves within about 20 minutes at 37 °C and 75 rpm in a medium of 0.5% Tween 20 in 50 mM sodium acetate buffer (pH 5.5) using a USP Apparatus 2. In another aspect, about 90% of the dosage form dissolves within about 30 minutes at 37 °C and 75 rpm in a medium of 0.5% Tween 20 in 50 mM sodium acetate buffer (pH 5.5) using a USP Apparatus 2. In another aspect, about 100% of the dosage form dissolves within about 40–45 minutes at 37 °C and 75 rpm in a medium of 0.5% Tween 20 in 50 mM sodium acetate buffer (pH 5.5) using a USP Apparatus 2.

[00102] Another embodiment described herein is a pharmaceutical composition for treating, prophylaxis, or amelioration of any type of pain, wherein the composition exhibits an in vitro dissolution rate comprising about 10% to about 90% dissolution after about 5 minutes to about 60 minutes at pH 4.5, including all integers and fractions within the specified ranges of dissolution and time. Another embodiment described herein is a pharmaceutical composition for treating, prophylaxis, or amelioration of any type of pain, wherein the composition exhibits an in vitro dissolution rate (% dissolution per minute) at pH 4.8, as described herein in Figure 6.

[00103] Another embodiment described herein is a method for manufacturing an oral pharmaceutical capsule dosage form comprising: (a) melting one or more suspension agents at a temperature of about 60 °C to 75 °C; (b) combining Compound 1 with the melted suspension agent of (a), blending the combination, and maintaining the blend at 60 °C to 75 °C; (c) encapsulating the blend in 2-piece hard capsules. In one aspect, the temperature is 65 °C. In one aspect, the

Compound 1 is micronized crystalline Form B. In one aspect, the suspension agent comprises tocopherol polyethylene glycol succinate (TPGS). Another embodiment described herein is an oral pharmaceutical capsule dosage form produced by the method described herein and illustrated in Figure 1. In one aspect, the oral pharmaceutical capsule dosage form comprises: (a) about 20% to about 80% by weight of Compound 1; (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the oral pharmaceutical capsule dosage form comprises: (a) about 20% to about 80% by weight of a crystalline form of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the oral pharmaceutical capsule dosage form comprises: (a) about 20% to about 80% by weight of a salt of Compound 1; and (b) about 20% to about 80% by weight of tocopherol polyethylene glycol succinate (TPGS). In one aspect, the dosage form comprises about 50 mg to about 750 mg of Compound 1. In one aspect, the dosage form comprises about 50 mg to about 750 mg of a crystalline form of Compound 1. In one aspect, the dosage form comprises about 50 mg to about 750 mg of a salt of Compound 1. In another aspect, the composition is effective at treating any type of pain in a subject in need thereof.

[00104] One embodiment described herein comprises a method for orally administering a dosage form that provides a total amount of Compound 1 of about 50 mg to about 1000 mg, including all integers within the specified range. One embodiment described herein comprises a method for orally administering a dosage form that provides a total amount of a crystalline form of Compound 1, of about 50 mg to about 1000 mg, including all integers within the specified range. One embodiment described herein comprises a method for orally administering a dosage form that provides a total amount of a salt of Compound 1, of about 50 mg to about 1000 mg, including all integers within the specified range.

[00105] In one embodiment described herein, the dosage form can comprise, but is not limited to, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 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,

about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, about 650 mg, about 660 mg, about 670 mg, about 680 mg, about 690 mg, about 700 mg, about 710 mg, about 720 mg, about 730 mg, about 740 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 810 mg, about 820 mg, about 830 mg, about 840 mg, about 850 mg, about 860 mg, about 870 mg, about 880 mg, about 890 mg, about 900 mg, about 910 mg, about 920 mg, about 930 mg, about 940 mg, about 950 mg, about 960 mg, about 970 mg, about 980 mg, about 990 mg, about 1000 mg, about 1250 mg, about 1500 mg, about 1750 mg, or about 2000 mg of Compound 1, or a salt or crystalline form thereof.

[00106] In one embodiment described here, the dosage form can comprise, but is not limited to, about 25 mg, about 50 mg, about 75 mg, 100 mg, about 125 mg, about 150 mg, about 175 mg about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 2625 mg, about 2650 mg, about 2675 mg, about 2700 mg, about 2725 mg, about 2750 mg, about 2775 mg, about 2800 mg, about 2825 mg, about 2850 mg, about 2875 mg, about 2900 mg, about 2925 mg, about 2950 mg, about 2975 mg, about 3000 mg, about 3025 mg, about 3050 mg, about 3075 mg, about

3100 mg, about 3125 mg, about 3150 mg, about 3175 mg, about 3200 mg, about 3225 mg, about 3250 mg, about 3275 mg, about 3300 mg, about 3325 mg, about 3350 mg, about 3375 mg, about 3400 mg, about 3425 mg, about 3450 mg, about 3475 mg, about 3500 mg, about 3525 mg, about 3550 mg, about 3575 mg, or about 3600 mg of one or more suspension agents. In another embodiment, the suspension agent is TPGS.

[00107] In another embodiment described herein, the dosage form can comprise, but is not limited to, about 50 mg to about 2000 mg. In another embodiment described herein, the dosage form can comprise, but is not limited to, about 50 mg to about 2000 mg of Compound 1. In another embodiment described herein, the dosage form can comprise, but is not limited to, about 50 mg to about 2000 mg of a salt of Compound 1. In another embodiment described herein, the dosage form can comprise, but is not limited to, about 50 mg to about 2000 mg of a crystalline form of Compound 1. In one aspect the dosage form can comprise about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, or about 2000 mg of Compound 1, or a salt or crystalline form thereof.

[00108] In another embodiment the daily dose of the pharmaceutical compositions described herein can comprise about 100 mg to about 4000 mg, including all integers within the specified range. In another embodiment the daily dose of the pharmaceutical compositions described herein can comprise about 100 mg to about 4000 mg of Compound 1, including all integers within the specified range. In another embodiment the daily dose of the pharmaceutical compositions described herein can comprise about 100 mg to about 4000 mg of a salt of Compound 1, including all integers within the specified range. In another embodiment the daily dose of the pharmaceutical compositions described herein can comprise about 100 mg to about 4000 mg of a crystalline form of Compound 1, including all integers within the specified range.

[00109] In one embodiment the daily dose of the pharmaceutical compositions described can comprise, but is not limited to, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about

600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2950 mg, about 3000 mg, about 3050 mg, about 3100 mg, about 3150 mg, about 3200 mg, about 3250 mg, about 3300 mg, about 3350 mg, about 3400 mg, about 3450 mg, about 3500 mg, about 3550 mg, about 3600 mg, about 3650 mg, about 3700 mg, about 3750 mg, about 3800 mg, about 3850 mg, about 3900 mg, about 3950 mg, about 4000 mg, or a greater amount of Compound 1 or a salt or crystalline form thereof.

[00110] In one embodiment, the daily dose of the pharmaceutical compositions described can comprise, but is not limited to, about 25 mg, about 50 mg, about 75 mg, 100 mg, about 125 mg, about 150 mg, about 175 mg about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about

2600 mg, about 2625 mg, about 2650 mg, about 2675 mg, about 2700 mg, about 2725 mg, about 2750 mg, about 2775 mg, about 2800 mg, about 2825 mg, about 2850 mg, about 2875 mg, about 2900 mg, about 2925 mg, about 2950 mg, about 2975 mg, about 3000 mg, about 3025 mg, about 3050 mg, about 3075 mg, about 3100 mg, about 3125 mg, about 3150 mg, about 3175 mg, about 3200 mg, about 3225 mg, about 3250 mg, about 3275 mg, about 3300 mg, about 3325 mg, about 3350 mg, about 3375 mg, about 3400 mg, about 3425 mg, about 3450 mg, about 3475 mg, about 3500 mg, about 3525 mg, about 3550 mg, about 3575 mg, or about 3600 mg, or a greater amount of one or more suspension agents. In one embodiment, the suspension agent is TPGS. In one embodiment, the daily dose of the pharmaceutical composition may comprise about of 25 mg to about 3600 mg of TPGS, or about 100 mg to about 3500 mg, or about 250 mg to about 3450 mg, or about 500 mg to about 3425 mg, or about 750 mg to about 3400 mg, or about 1000 mg to about 3375 mg, or about 1100 mg to about 3350 mg, or about 1200 mg to about 3325 mg, or about 1300 mg to about 3300 mg, or about 1400 mg to about 3275 mg, or about 1500 mg to about 3250 mg, or about 1600 mg to about 3325 mg, or about 1700 mg to about 3300 mg, or about 1800 mg to about 3275 mg, or about 1900 mg to about 3250 mg, or about 2000 mg to about 3200 mg, or any integer between 25 mg and 3600 mg, or no more than about 4000 mg, or no more than about 3900 mg, or no more than about 3800 mg, or no more than about 3700 mg, or no more than about 3600 mg, or no more than about 3500 mg, or no more than about 3400 mg, or no more than about 3300 mg, or no more than about 3200 mg, or no more than about 3100 mg, or no more than about 3000 mg.

[00111] The dosage form can be administered, for example, 1×, 2×, 3×, 4×, 5×, 6×, or even more times per day. One or more dosage forms can be administered, for example, for 1, 2, 3, 4, 5, 6, 7 days, or even longer. One or more dosage forms can be administered, for example, for 1, 2, 3, 4 weeks, or even longer. One or more dosage forms can be administered, for example, for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, 1 year, 2, years, 3 years, 4 years, 5 years, over 5 years, a decade, multiple decades, or even longer. One or more dosage forms can be administered at a regular interval until the subject or subject in need thereof, does not require treatment, prophylaxis, or amelioration of any disease or condition, including but not limited to, pain.

[00112] In one embodiment, the pharmaceutical composition described herein is administered as a unit dose at various times throughout a 24-hour period to achieve a total daily dosage. In some embodiments, the pharmaceutical composition is administered as a unit dose

once per day (QD), twice per day (BID), three times per day (TID), four times per day (QID), a greater number of times per day, or as needed (PRN), to alleviate pain, for example.

[00113] In one embodiment, the pharmaceutical composition described herein is administered in multiple dosages simultaneously or sequentially over a finite period of time. For example, two or more identical dosages are administered at one time to achieve a specific dose. In another embodiment, two or more different dosages are administered at one time to achieve a specific dose. In another embodiment, one dose is administered at t_0 and another dose is administered at t_n, where n is a period of time 5 min to 24 hours after t_0 and the individual or simultaneous doses may be identical or different. Such dual or different simultaneous or sequential doses can be used to provide a unit dose of the pharmaceutical composition to a subject in need thereof. The administration can be once per day (QD), twice per day (BID), three times per day (TID), four times per day (QID), a greater number of times per day, or as needed (PRN), to alleviate pain.

[00114] In one embodiment, the pharmaceutical composition described herein provides a dosage of Compound 1 or a salt or crystalline form thereof for administration to a subject. The dosage form can be administered, for example, to a subject, or a subject in need thereof. As used herein, "a subject in need thereof" is a subject susceptible to or experiencing pain. In one aspect, the subject is a mammal, or a mammal in need thereof. In one aspect, the subject is a human, or human in need thereof. In one aspect, the human or human in need thereof is a medical patient. In one aspect, the human subject is a child (~0–9 years old) or an adolescent (~10–17 years old). In one aspect, the subject is from about 0 to about 9 years of age. In another aspect, the human subject is from about 10 years to about 17 years of age. In another aspect, the human subject is over 17 years of age. In another aspect, the human subject is an adult (≥18 years of age).

[00115] Another embodiment described herein, is a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof comprising administering an effective amount of the pharmaceutical composition described herein to the subject in the fasted state or where the subject has not consumed food or non-clear liquids for about 4 to 6 hours.

[00116] Another embodiment described herein, is a method for treating any type of pain in a subject in need thereof comprising administering an effective amount of the pharmaceutical

composition described herein to the subject in the fed state or where the subject has consumed food or non-clear liquids within about 4 to 6 hours.

[00117] In another embodiment, a method for treating any type of pain in a subject in need thereof comprises administering an effective amount of the pharmaceutical composition described herein to the subject where the subject has not consumed dairy products for about 4 to 6 hours prior to administration and abstains from dairy products for about 4 to 6 hours after administration.

[00118] In another embodiment, a method for treating any type of pain in a subject in need thereof comprises administering an effective amount of the pharmaceutical composition described herein to the subject where the subject has not consumed dairy products for about 3 to 5 hours prior to administration and abstains from dairy products for about 3 to 5 hours after administration. In another embodiment, the subject has not consumed dairy products for about 2 to 4 hours prior to administration and abstains from dairy products for about 2 to 4 hours after administration. In another embodiment, the subject has not consumed dairy products for about 1 to 3 hours prior to administration and abstains from dairy products for about 1 to 2 hours after administration. In another embodiment, the subject has not consumed dairy products for about 30 minutes to 1 hour prior to administration and abstains from dairy products for about 30 minutes to 1 hour after administration. In another embodiment, the subject has not consumed dairy products for at least about 30 minutes prior to administration and abstains from dairy products for at least about 30 minutes after administration.

[00119] In another embodiment, a method for treating any type of pain in a subject in need thereof comprises administering an effective amount of the pharmaceutical composition described herein to the subject where the subject limits consumption of dairy products for about 4 to 6 hours prior to administration and for about 4 to 6 hours after administration. In another embodiment, the subject limits consumption of dairy products for about 3 to 5 hours prior to administration and for about 3 to 5 hours after administration. In another embodiment, the subject limits consumption of dairy products for about 2 to 4 hours prior to administration and for about 2 to 4 hours after administration. In another embodiment, the subject limits consumption of dairy products for about 1 to 3 hours prior to administration and for about 1 to 2 hours after administration. In another embodiment, the subject limits consumption of dairy products for about 30 minutes to 1 hour prior to administration and for about 30 minutes to 1 hour after administration. In another embodiment,

the subject limits consumption of dairy products for at least about 30 minutes prior to administration and for at least about 30 minutes after administration.

[00120] In another embodiment, a method for treating any type of pain in a subject in need thereof comprises administering an effective amount of the pharmaceutical composition described herein to the subject where the subject has consumed a limited amount of dairy products for about 3 to 5 hours prior to administration and abstains from dairy products for about 3 to 5 hours after administration. In another embodiment, the subject has consumed a limited amount of dairy products for about 2 to 4 hours prior to administration and abstains from dairy products for about 2 to 4 hours after administration. In another embodiment, the subject has consumed a limited amount of dairy products for about 1 to 3 hours prior to administration and abstains from dairy products for about 1 to 2 hours after administration. In another embodiment, the subject has consumed a limited amount of dairy products for about 30 minutes to 1 hour prior to administration and abstains from dairy products for about 30 minutes to 1 hour after administration. In another embodiment, the subject has consumed a limited amount of dairy products for at least about 30 minutes prior to administration and abstains from dairy products for at least about 30 minutes after administration.

[00121] In another embodiment, a method for treating any type of pain in a subject in need thereof comprises administering an effective amount of the pharmaceutical composition described herein to the subject where the subject has consumed a limited amount of dairy products for about 3 to 5 hours prior to administration and a limited amount of dairy products for about 3 to 5 hours after administration. In another embodiment, the subject has consumed a limited amount of dairy products for about 2 to 4 hours prior to administration and a limited amount of dairy products for about 2 to 4 hours after administration. In another embodiment, the subject has consumed a limited amount of dairy products for about 1 to 3 hours prior to administration and a limited amount of dairy products for about 1 to 2 hours after administration. In another embodiment, the subject has consumed a limited amount of dairy products for about 30 minutes to 1 hour prior to administration and a limited amount of dairy products for about 30 minutes to 1 hour after administration. In another embodiment, the subject has consumed a limited amount of dairy products for at least about 30 minutes prior to administration and a limited amount of dairy products for at least about 30 minutes after administration.

[00122] In one embodiment, is a pharmaceutical dosage form that upon ingestion by a subject provides for one or more pharmacokinetic parameters such as C_{max}, T_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, $t_{½}$, or an elimination rate constant.

[00123] In another embodiment, is a method for treating any type of pain in a subject in need thereof comprising administering an effective amount of a pharmaceutical composition described herein that upon ingestion by a subject provides for one or more pharmacokinetic parameters such as C_{max}, T_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, $t_{½}$, or an elimination rate constant.

[00124] Another embodiment described herein, is a pharmaceutical composition comprising any of the compositions or formulations described herein or shown in the Tables or Examples described herein. Any of the components described herein or shown in the Tables or Examples can be increased, decreased, combined, added to, recombined, switched, or removed to provide for a formulation comprising about 100% by weight.

[00125] As described herein, the pharmaceutically acceptable compositions can comprise pharmaceutically acceptable carriers, adjuvants, or vehicles, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's *Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds described herein, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of the embodiments described herein. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch;

cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00126] Another embodiment described herein is a kit for dispensing the oral pharmaceutical dosage form produced by any of the compositions or the methods described herein comprising: (a) at least one dosage form comprising micronized crystalline form B of Compound 1; (b) at least one moisture proof dispensing receptacle comprising blister or strip packs, an aluminum blister, a transparent or opaque polymer blister with pouch, polypropylene tubes, colored blister materials, tubes, bottles, and bottles optionally containing a child-resistant feature, optionally comprising a desiccant, such as a molecular sieve or silica gel; and optionally (c) an insert comprising instructions or prescribing information for Compound 1 comprised by the oral pharmaceutical composition; or (d) directions for administration or any contraindications. In one aspect described herein, the kit is useful for treating any type of pain or a medical condition according to any of the methods described herein.

[00127] Another embodiment described herein, is a compound that is an inhibitor of voltage-gated sodium channels. Compound 1 or salts thereof is useful for the treatment of diseases, disorders, and conditions including, but not limited to chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia. One aspect described herein is a pharmaceutical composition comprising Compound 1 and optionally a pharmaceutically acceptable carrier, adjuvant, or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[00128] In another embodiment, the compounds and compositions of the present invention are useful for treating neurodegenerative diseases. In one embodiment, the neurodegenerative disease is multiple sclerosis. In another embodiment, the neurodegenerative disease is a genetic form of autism called Pitt Hopkins Syndrome (PTHS).

[00129] Another embodiment described herein is a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain known in the art in a subject in need thereof comprising administering an effective amount of the composition to a subject in need thereof.

[00130] Another embodiment described herein is a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain known in the art (including any type of pain treated by any of the methods described herein) in a subject in need thereof comprising administering to the subject an effective amount of a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and tocopherol polyethylene glycol succinate (TPGS), wherein the total amount of TPGS administered to the subject is about 25 mg to about 3600 mg per day, or about 100 mg to about 3500 mg per day, or about 250 mg to about 3450 mg per day, or about 500 mg to about 3425 mg per day, or about 750 mg to about 3400 mg per day, or about 1000 mg to about 3375 mg per day, or about 1100 mg to about 3350 mg per day, or about 1200 mg to about 3325 mg per day, or about 1300 mg to about 3300 mg per day, or about 1400 mg to about 3275 mg per day, or about 1500 mg to about 3250 mg per day, or about 1600 mg to about 3325 mg per day, or about 1700 mg to about 3300 mg per day, or about 1800 mg to about 3275 mg per day, or about 1900 mg to about 3250 mg per day, or about 2000 mg to about 3200 mg per day, or any integer between 25 mg and 3600 mg per day, or no more than about 4000 mg per day, or no more than about 3900 mg per day, or no more than about 3800 mg per day, or no more than about 3700 mg per day, or no more than about 3600 mg per day, or no more than about 3500 mg per day, or no more than about 3400 mg per day, or no more than about 3300 mg per day, or no more than about 3200 mg per day, or no more than about 3100 mg per day, or no more than about 3000 mg per day.

[00131] Another embodiment described herein is a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain known in the art (including any type of pain treated by any of the methods described herein) in a subject in need thereof comprising administering to the subject an effective amount of a pharmaceutical

composition comprising Compound 1 and tocopherol polyethylene glycol succinate (TPGS), wherein the total amount of TPGS administered to the subject is about 25 mg to about 3600 mg per day, or about 100 mg to about 3500 mg per day, or about 250 mg to about 3450 mg per day, or about 500 mg to about 3425 mg per day, or about 750 mg to about 3400 mg per day, or about 1000 mg to about 3375 mg per day, or about 1100 mg to about 3350 mg per day, or about 1200 mg to about 3325 mg per day, or about 1300 mg to about 3300 mg per day, or about 1400 mg to about 3275 mg per day, or about 1500 mg to about 3250 mg per day, or about 1600 mg to about 3325 mg per day, or about 1700 mg to about 3300 mg per day, or about 1800 mg to about 3275 mg per day, or about 1900 mg to about 3250 mg per day, or about 2000 mg to about 3200 mg per day, or any integer between 25 mg and 3600 mg per day, or no more than about 4000 mg per day, or no more than about 3900 mg per day, or no more than about 3800 mg per day, or no more than about 3700 mg per day, or no more than about 3600 mg per day, or no more than about 3500 mg per day, or no more than about 3400 mg per day, or no more than about 3300 mg per day, or no more than about 3200 mg per day, or no more than about 3100 mg per day, or no more than about 3000 mg per day.

[00132] In one aspect, the pain comprises one or more of abdominal pain, abnormal gastrointestinal motility pain, acute herpes zoster pain, acute inflammatory pain, acute intermittent pain, acute musculoskeletal pain, acute obstetric pain, acute pain, acute post-operative pain (e.g., bunionectomy pain; abdominoplasty pain; knee pain from a total knee replacement; hip pain from a total hip replacement; pain from a laminectomy; pain from a hernia repair; or hemorrhoid removal pain), acute tendonitis pain, acute visceral pain, adiposis dolorosa pain, amyotrophic lateral sclerosis pain, angina-induced pain, anti-retroviral therapy induced neuralgia, anxiety pain, appendicitis pain, arrhythmia pain, arthritis pain, ataxia pain, back pain, Behçet's disease pain, bipolar disorder pain, bladder and urogenital disease pain, bone pain, brachial plexus avulsion injury pain, breakthrough pain, burn pain, burning mouth syndrome pain, bursitis pain, cancer chemotherapy induced neuralgia, cancer pain, cardiac arrhythmia pain, cardiac pain, carpal tunnel syndrome pain, central pain, cerebral ischemia, Cesarean-section pain, Charcot-Marie Tooth neuropathic pain, chemotherapy induced neuropathic pain, chest pain, cholecystitis pain, chronic and acute headache pain, chronic and acute neuropathic pain, chronic arthritis, chronic pain, chronic visceral pain, cluster headache pain, cold pain, complex regional pain syndrome, Crohn's disease pain, dental pain (e.g., third molar extraction), depression pain, diabetic neuralgia, diabetic

neuropathic pain, diabetic peripheral neuropathic pain, drug therapy induced neuralgia, ectopic proximal and distal discharge pain, endometriosis pain, epilepsy pain, erythromelalgia pain, exercise induced angina pain, exercise induced pain, exercise pain, Fabry's disease pain, femur cancer pain, fibromyalgia pain, general neuralgias, granuloma annulare pain, Guillain-Barre pain, gut pain, Haglund syndrome pain, head pain, headache pain, hereditary sensory neuropathic pain, hernia pain, herpetic neuralgia pain, HIV-associated neuropathic pain, HIV-associated sensory neuropathic pain, hyperactivity bladder pain, hypertension pain, idiopathic pain, idiopathic sensory neuropathic pain, idiopathic small-fiber neuropathic pain, incontinence pain, inflammatory bowel disease pain, inflammatory pain, injury pain, interstitial cystitis (IC) pain, intestinal obstruction pain, intractable pain, irritable bowel syndrome pain, joint pain, labor pain, leprosy pain, lipoidica pain, malignancy pain, mechanical low back pain, migraine pain, Morton's neuroma pain, movement disorder pain, multiple sclerosis (MS) pain, musculoskeletal pain, myofascial pain syndrome pain, myotonia pain, neck pain, necrobiosis pain, nerve avulsion injury pain, nerve entrapment injury pain, neurodegenerative disorder pain, neuroendocrine disorder pain, neuropathic low back pain, neuropathic pain, nociceptive pain, non-malignant chronic bone pain, orofacial pain, osteoarthritis pain, painful bladder syndrome, painful legs, painful moving toes, painful neuromas, palpitations, pancreatic pain, paroxysmal extreme pain, pathological cough pain, pelvic pain, peripheral nerve injury pain, phantom pain, phlebitic pain, post spinal cord injury pain, post-amputation pain, post-herpetic neuralgia, post-mastectomy pain, post-stroke pain, postsurgical pain, premenstrual pain, prostatitis pain, pruritis pain, psychiatric disorder associated pain, pyelonephritis pain, radicular pain, radiculopathy, radiotherapy-induced neuropathic pain, renal colic pain, rheumatoid arthritis pain, sarcoidosis pain, sciatica pain, severe pain, shingles pain, sickle cell anemia pain, sinusitis pain, spinal cord injury pain, spinal stenosis pain, sports injury pain, stress-induced angina pain, stress-induced pain, stroke pain, temporomandibular joint pain, tendonitis pain, tension headache pain, thalamic pain, tinnitus pain, trauma pain, traumatic brain injury pain, traumatic neuroma, trigeminal autonomic cephalalgia, trigeminal neuralgia, urinary incontinence pain, visceral pain, widespread pain, or other types of pain.

[00133] In one embodiment the pain comprises acute pain including bunionectomy pain, abdominoplasty pain, orthopedic procedure pain (e.g., total knee replacement, total hip replacement and laminectomy), hernia pain, hemorrhoid pain, or dental pain (e.g., third molar extractions).

[00134] In another embodiment the pain comprises chronic pain including diabetic peripheral neuropathy pain, trigeminal neuralgia, rheumatoid or osteoarthritis pain, chronic lower back pain, post-herpetic neuralgia, or radiculopathy pain.

[00135] Another embodiment described herein comprises a method of treating or lessening the severity in a subject of acute pain, chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia comprising administering an effective amount of a compound to the subject, or a pharmaceutical composition of crystalline form B of Compound 1.

[00136] Another embodiment described herein comprises a method of treating or lessening the severity in a subject of acute pain, chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia comprising administering an effective amount of a compound to the subject, or a pharmaceutical composition of crystalline form B of Compound 1.

[00137] Another embodiment described herein comprises a method of treating or lessening the severity in a subject of gut pain, including inflammatory bowel disease pain, Crohn's disease pain or interstitial cystitis pain comprising administering an effective amount of a pharmaceutical composition of Compound 1.

[00138] Another embodiment described herein comprises a method of treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma, traumatic neuroma, Morton's neuroma, nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury, complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia comprising administering an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00139] Another embodiment described herein comprises a method of treating or lessening the severity of musculoskeletal pain, such as osteoarthritis pain, back pain, cold pain, burn pain or

dental pain comprising administering an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00140] Another embodiment described herein comprises a method of treating or lessening the severity of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain or vulvodynia comprising administering an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00141] Another embodiment described herein comprises a method of treating or lessening the severity of inflammatory pain, such as rheumatoid arthritis pain comprising administering an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00142] Another embodiment described herein comprises a method of treating or lessening the severity of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain comprising administering an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00143] Another embodiment described herein comprises a method of treating or lessening the severity of pathological cough comprising administering an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00144] Another embodiment described herein comprises a method of treating or lessening the severity of trigeminal neuralgia or herpetic neuralgia comprising administering an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00145] In some embodiments, the pain comprises musculoskeletal pain. In some embodiments, the musculoskeletal pain comprises osteoarthritis pain. In some embodiments, the pain comprises neuropathic pain. In some embodiments, the neuropathic pain comprises idiopathic small-fiber neuropathy. As used herein, the phrase "idiopathic small-fiber neuropathy" includes any small fiber neuropathy. In some embodiments, the neuropathic pain comprises small-fiber neuropathy.

[00146] In some embodiments, the pain comprises acute pain. In some embodiments, the acute pain comprises acute post-operative pain. In some embodiments, the pain comprises postsurgical pain.

[00147] Another embodiment described herein comprises a method wherein the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with an effective amount of Compound 1, or a pharmaceutical composition thereof.

[00148] Another embodiment described herein comprises the use of a compound or pharmaceutical composition of Compound 1 for the manufacture of a medicament for use in treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain.

[00149] Another embodiment described herein comprises the use of a compound or pharmaceutical composition of Compound 1 for the manufacture of a medicament for use in treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain.

[00150] Another embodiment described herein comprises the use of a compound or pharmaceutical composition of Compound 1 for the manufacture of a medicament for use in treating or lessening the severity in a subject of pathological cough.

[00151] Another embodiment described herein comprises the use of a compound or pharmaceutical composition of Compound 1 for the manufacture of a medicament in combination with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

[00152] Another embodiment described herein comprises the use of a compound or pharmaceutical composition of Compound 1 for the manufacture of a medicament for use in treating or lessening the severity of acute pain, chronic pain, neuropathic pain, inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, dipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, pathological cough, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head pain, neck pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, cancer pain, stroke, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress induced angina, exercise induced angina, palpitations, hypertension, or abnormal gastro-intestinal motility.

[00153] Another embodiment described herein comprises the use of a compound or pharmaceutical composition of Compound 1 for the manufacture of a medicament for use in treating or lessening the severity of abdominal pain, abnormal gastrointestinal motility pain, acute herpes zoster pain, acute inflammatory pain, acute intermittent pain, acute musculoskeletal pain,

acute obstetric pain, acute pain, acute post-operative pain (e.g., bunionectomy pain; abdominoplasty pain; knee pain from a total knee replacement; hip pain from a total hip replacement; pain from a laminectomy; pain from a hernia repair; or hemorrhoid removal pain), acute tendonitis pain, acute visceral pain, adiposis dolorosa pain, amyotrophic lateral sclerosis pain, angina-induced pain, anti-retroviral therapy induced neuralgia, anxiety pain, appendicitis pain, arrhythmia pain, arthritis pain, ataxia pain, back pain, Behçet's disease pain, bipolar disorder pain, bladder and urogenital disease pain, bone pain, brachial plexus avulsion injury pain, breakthrough pain, burn pain, burning mouth syndrome pain, bursitis pain, cancer chemotherapy induced neuralgia, cancer pain, cardiac arrhythmia pain, cardiac pain, carpal tunnel syndrome pain, central pain, cerebral ischemia, Cesarean-section pain, Charcot-Marie Tooth neuropathic pain, chemotherapy induced neuropathic pain, chest pain, cholecystitis pain, chronic and acute headache pain, chronic and acute neuropathic pain, chronic arthritis, chronic pain, chronic visceral pain, cluster headache pain, cold pain, complex regional pain syndrome, Crohn's disease pain, dental pain (e.g., third molar extraction), depression pain, diabetic neuralgia, diabetic neuropathic pain, diabetic peripheral neuropathic pain, drug therapy induced neuralgia, ectopic proximal and distal discharge pain, endometriosis pain, epilepsy pain, erythromelalgia pain, exercise induced angina pain, exercise induced pain, exercise pain, Fabry's disease pain, femur cancer pain, fibromyalgia pain, general neuralgias, granuloma annulare pain, Guillain-Barre pain, gut pain, Haglund syndrome pain, head pain, headache pain, hereditary sensory neuropathic pain, hernia pain, herpetic neuralgia pain, HIV-associated neuropathic pain, HIV-associated sensory neuropathic pain, hyperactivity bladder pain, hypertension pain, idiopathic pain, idiopathic sensory neuropathic pain, idiopathic small-fiber neuropathic pain, incontinence pain, inflammatory bowel disease pain, inflammatory pain, injury pain, interstitial cystitis (IC) pain, interstitial cystitis pain, intestinal obstruction pain, intractable pain, irritable bowel syndrome pain, joint pain, labor pain, leprosy pain, lipoidica pain, malignancy pain, mechanical low back pain, migraine pain, Morton's neuroma pain, movement disorder pain, multiple sclerosis (MS) pain, musculoskeletal pain, myofascial pain syndrome pain, myotonia pain, neck pain, necrobiosis pain, nerve avulsion injury pain, nerve entrapment injury pain, neurodegenerative disorder pain, neuroendocrine disorder pain, neuropathic low back pain, neuropathic pain, nociceptive pain, non-malignant chronic bone pain, orofacial pain, osteoarthritis pain, painful bladder syndrome, painful legs, painful moving toes, painful neuromas, palpitations, pancreatic pain, paroxysmal extreme pain, pathological cough

pain, pelvic pain, peripheral nerve injury pain, phantom pain, phlebitic pain, post spinal cord injury pain, post-amputation pain, post-herpetic neuralgia, post-mastectomy pain, post-stroke pain, postsurgical pain, premenstrual pain, prostatitis pain, pruritis pain, psychiatric disorder associated pain, pyelonephritis pain, radicular pain, radiculopathy, radiotherapy-induced neuropathic pain, renal colic pain, rheumatoid arthritis pain, sarcoidosis pain, sciatica pain, severe pain, shingles pain, sickle cell anemia pain, sinusitis pain, spinal cord injury pain, spinal stenosis pain, sports injury pain, stress-induced angina pain, stress-induced pain, stroke pain, temporomandibular joint pain, tendonitis pain, tension headache pain, thalamic pain, tinnitus pain, trauma pain, traumatic brain injury pain, traumatic neuroma, trigeminal autonomic cephalalgia, trigeminal neuralgia, urinary incontinence pain, visceral pain, widespread pain, or other types of pain. In one aspect, the pain comprises osteoarthritis or rheumatoid arthritis pain. In another aspect, the pain comprises trigeminal neuralgia or herpetic neuralgia.

[00154] Another embodiment described herein comprises the use of a compound or pharmaceutical composition of Compound 1 for the manufacture of a medicament for use in treating or lessening the severity of neuropathic pain. In one aspect, the neuropathic pain is selected from post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma, traumatic neuroma, Morton's neuroma, nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain, nerve avulsion injury, brachial plexus avulsion, complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

[00155] Another embodiment described herein is pharmaceutical composition for use in a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain known in the art (including any type of pain treated by any of the methods described herein) in a subject in need thereof comprising administering to the subject an effective amount of the pharmaceutical composition, wherein the pharmaceutical composition comprises Compound 1, or a pharmaceutically acceptable salt thereof, and tocopherol polyethylene glycol succinate (TPGS), and wherein the total amount of TPGS administered to the subject is about 25 mg to about 3600 mg per day, or about 100 mg to about 3500 mg per day, or

about 250 mg to about 3450 mg per day, or about 500 mg to about 3425 mg per day, or about 750 mg to about 3400 mg per day, or about 1000 mg to about 3375 mg per day, or about 1100 mg to about 3350 mg per day, or about 1200 mg to about 3325 mg per day, or about 1300 mg to about 3300 mg per day, or about 1400 mg to about 3275 mg per day, or about 1500 mg to about 3250 mg per day, or about 1600 mg to about 3325 mg per day, or about 1700 mg to about 3300 mg per day, or about 1800 mg to about 3275 mg per day, or about 1900 mg to about 3250 mg per day, or about 2000 mg to about 3200 mg per day, or any integer between 25 mg and 3600 mg per day, or no more than about 4000 mg per day, or no more than about 3900 mg per day, or no more than about 3800 mg per day, or no more than about 3700 mg per day, or no more than about 3600 mg per day, or no more than about 3500 mg per day, or no more than about 3400 mg per day, or no more than about 3300 mg per day, or no more than about 3200 mg per day, or no more than about 3100 mg per day, or no more than about 3000 mg per day.

[00156] Another embodiment described herein is a pharmaceutical composition for use in a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain known in the art (including any type of pain treated by any of the methods described herein) in a subject in need thereof comprising administering to the subject an effective amount of the pharmaceutical composition, wherein the pharmaceutical composition comprises Compound 1 and tocopherol polyethylene glycol succinate (TPGS), and wherein the total amount of TPGS administered to the subject is about 25 mg to about 3600 mg per day, or about 100 mg to about 3500 mg per day, or about 250 mg to about 3450 mg per day, or about 500 mg to about 3425 mg per day, or about 750 mg to about 3400 mg per day, or about 1000 mg to about 3375 mg per day, or about 1100 mg to about 3350 mg per day, or about 1200 mg to about 3325 mg per day, or about 1300 mg to about 3300 mg per day, or about 1400 mg to about 3275 mg per day, or about 1500 mg to about 3250 mg per day, or about 1600 mg to about 3325 mg per day, or about 1700 mg to about 3300 mg per day, or about 1800 mg to about 3275 mg per day, or about 1900 mg to about 3250 mg per day, or about 2000 mg to about 3200 mg per day, or any integer between 25 mg and 3600 mg per day, or no more than about 4000 mg per day, or no more than about 3900 mg per day, or no more than about 3800 mg per day, or no more than about 3700 mg per day, or no more than about 3600 mg per day, or no more than about 3500 mg per day, or no more than about 3400 mg per day, or no more than about 3300 mg per day, or no more than

about 3200 mg per day, or no more than about 3100 mg per day, or no more than about 3000 mg per day.

[00157] Another embodiment described herein is pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and tocopherol polyethylene glycol succinate (TPGS), for use in a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain known in the art (including any type of pain treated by any of the methods described herein) in a subject in need thereof, wherein the pharmaceutical composition is prepared for administration to the subject of Compound 1, or a pharmaceutically acceptable salt thereof, and TPGS, wherein the total amount of TPGS administered to the subject is about 25 mg to about 3600 mg per day, or about 100 mg to about 3500 mg per day, or about 250 mg to about 3450 mg per day, or about 500 mg to about 3425 mg per day, or about 750 mg to about 3400 mg per day, or about 1000 mg to about 3375 mg per day, or about 1100 mg to about 3350 mg per day, or about 1200 mg to about 3325 mg per day, or about 1300 mg to about 3300 mg per day, or about 1400 mg to about 3275 mg per day, or about 1500 mg to about 3250 mg per day, or about 1600 mg to about 3325 mg per day, or about 1700 mg to about 3300 mg per day, or about 1800 mg to about 3275 mg per day, or about 1900 mg to about 3250 mg per day, or about 2000 mg to about 3200 mg per day, or any integer between 25 mg and 3600 mg per day, or no more than about 4000 mg per day, or no more than about 3900 mg per day, or no more than about 3800 mg per day, or no more than about 3700 mg per day, or no more than about 3600 mg per day, or no more than about 3500 mg per day, or no more than about 3400 mg per day, or no more than about 3300 mg per day, or no more than about 3200 mg per day, or no more than about 3100 mg per day, or no more than about 3000 mg per day.

[00158] Another embodiment described herein is pharmaceutical composition comprising Compound 1, and tocopherol polyethylene glycol succinate (TPGS), for use in a method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain known in the art (including any type of pain treated by any of the methods described herein) in a subject in need thereof, wherein the pharmaceutical composition is prepared for administration to the subject of Compound 1 and TPGS, wherein the total amount of TPGS administered to the subject is about 25 mg to about 3600 mg per day, or about 100 mg to about 3500 mg per day, or about 250 mg to about 3450 mg per day, or about 500 mg to about 3425 mg per day, or about 750 mg to about 3400 mg per day, or about 1000 mg to about 3375 mg per day,

or about 1100 mg to about 3350 mg per day, or about 1200 mg to about 3325 mg per day, or about 1300 mg to about 3300 mg per day, or about 1400 mg to about 3275 mg per day, or about 1500 mg to about 3250 mg per day, or about 1600 mg to about 3325 mg per day, or about 1700 mg to about 3300 mg per day, or about 1800 mg to about 3275 mg per day, or about 1900 mg to about 3250 mg per day, or about 2000 mg to about 3200 mg per day, or any integer between 25 mg and 3600 mg per day, or no more than about 4000 mg per day, or no more than about 3900 mg per day, or no more than about 3800 mg per day, or no more than about 3700 mg per day, or no more than about 3600 mg per day, or no more than about 3500 mg per day, or no more than about 3400 mg per day, or no more than about 3300 mg per day, or no more than about 3200 mg per day, or no more than about 3100 mg per day, or no more than about 3000 mg per day.

[00159] As used herein a "therapeutically effective amount" of the compound, or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.

[00160] Another embodiment described herein is the use of a compound, salt, pharmaceutical composition, or pharmaceutical dosage form described herein for the manufacture of a medicament for use in one or more of the foregoing methods.

[00161] The compounds and pharmaceutically acceptable compositions described herein can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated." For example, exemplary additional therapeutic agents include, but are not limited to: nonopioid analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin;

naphthylalkanones such as Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproxen sodium, Oxaprozin; salicylates such as Aspirin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine, Butorphanol, Dezocine, Nalbuphine, and Pentazocine). Additionally, nondrug analgesic approaches may be utilized in conjunction with administration of one or more compounds described herein. For example, anesthesiologic (intraspinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in *The Merck Manual*, Nineteenth Edition, Ed. Robert S. Porter and Justin L. Kaplan, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., (2011), and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[00162] In one embodiment, appropriate therapeutic agents are selected from the following:

[00163] an opioid analgesic, e.g., morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, or pentazocine;

[00164] a nonsteroidal antiinflammatory drug (NSAID), e.g., aspirin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;

[00165] a barbiturate sedative, e.g., amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, thiamylal or thiopental;

[00166] a benzodiazepine having a sedative action, e.g., chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;

[00167] a histamine (H_1) antagonist having a sedative action, e.g., diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;

[00168] a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;

[00169] a skeletal muscle relaxant, e.g., baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadine;

[00170] an NMDA receptor antagonist, e.g., dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2- piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g., ifenprodil, traxoprodil or (−)-(*R*)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-l- piperidinyl]-l-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone;

[00171] an alpha-adrenergic, e.g., doxazosin, tamsulosin, clonidine, guanfacine, dexmedetomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-l, 2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

[00172] a tricyclic antidepressant, e.g., desipramine, imipramine, amitriptyline or nortriptyline;

[00173] an anticonvulsant, e.g., carbamazepine (Tegretol®), lamotrigine, topiramate, lacosamide (Vimpat®) or valproate;

[00174] a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g., (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11 -tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[l,4]diazocino[2,l-g][l,7]-naphthyridine-6-13-dione (TAK-637), 5- [[(2*R*,3*S*)-2-[(lR)-l-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-l,2-dihydro-3H-l,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2*S*,3*S*);

[00175] a muscarinic antagonist, e.g., oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;

[00176] a COX-2 selective inhibitor, e.g., celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;

[00177] a coal-tar analgesic, in particular paracetamol;

[00178] a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, belaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;

[00179] a vanilloid receptor agonist (e.g., resiniferatoxin or civamide) or antagonist (e.g., capsazepine, GRC-15300);

[00180] a beta-adrenergic such as propranolol;

[00181] a local anesthetic such as mexiletine;

[00182] a corticosteroid such as dexamethasone;

[00183] a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;

[00184] a 5-HT_{2A} receptor antagonist such as *R*(+)-alpha-(2,3-dimethoxy-phenyl)-l-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);

[00185] a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (*E*)-N-methyl-4-(3-pyridinyl)-3-buten-l-amine (RJR-2403), (*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

[00186] Tramadol®, Tramadol ER (Ultram ER®), Tapentadol ER (Nucynta®);

[00187] a PDE5 inhibitor, such as 5-[2-ethoxy-5-(4-methyl-l-piperazinyl-sulphonyl)phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6*R*,12a*R*)- 2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',l':6,l]-pyrido[3,4-b]indole-l,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-l-yl-l-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,l-f][l,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(l-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(l-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pvrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-l-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H- pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2*S*)-2-(hydroxymethyl)pyrrolidin-

l-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(l- methyl-7-oxo-3-propyl-6,7-dihydro-lH-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(l-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

[00188] an alpha-2-delta ligand such as gabapentin (Neurontin®), gabapentin GR (Gralise®), gabapentin, enacarbil (Horizant®), pregabalin (Lyrica®), 3-methyl gabapentin, (l[alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3*S*,5*R*)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3*S*,5*R*)-3-amino-5-methyl-octanoic acid, (2*S*,4*S*)-4-(3-chlorophenoxy)proline, (2*S*,4*S*)-4-(3-fluorobenzyl)-proline, [(l*R*,5*R*,6*S*)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(l-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3*S*,4*S*)-(l-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3*S*,5*R*)-3-aminomethyl-5-methyl-octanoic acid, (3*S*,5*R*)-3-amino-5-methyl-nonanoic acid, (3*S*,5*R*)-3-amino-5-methyl-octanoic acid, (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-heptanoic acid and (3*R*,4*R*,5*R*)-3-amino-4,5-dimethyl-octanoic acid;

[00189] a cannabinoid such as KHK-6188;

[00190] a metabotropic glutamate subtype 1 receptor (mGluRl) antagonist;

[00191] a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, D,L-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;

[00192] a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (*S*,*S*)-reboxetine;

[00193] a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine (Cymbalta®), milnacipran and imipramine;

[00194] an inducible nitric oxide synthase (iNOS) inhibitor such as *S*-[2-[(l-iminoethyl)amino]ethyl]-L-homocysteine, *S*-[2-[(l-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, *S*-[2-[(l-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2*S*,5*Z*)-2-amino-2-methyl-7-[(l-

iminoethyl)amino]-5-heptenoic acid, 2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-*S*-chloro-*S*-pyridinecarbonitrile; 2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2*S*,4*R*)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[(1*R*,3*S*)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, NXN-462, or guanidinoethyldisulfide;

[00195] an acetylcholinesterase inhibitor such as donepezil;

[00196] a prostaglandin E2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(15)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;

[00197] a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP- 105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870;

[00198] a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone (CV-6504);

[00199] a sodium channel blocker, such as lidocaine, lidocaine plus tetracaine cream (ZRS-201) or eslicarbazepine acetate;

[00200] a Nav1.7 blocker, such as XEN-402, XEN403, TV-45070, PF-05089771, CNV1014802, GDC-0276, RG7893, RG6029/GDC-0310, DSP-2230, and those such as disclosed in WO 2011/140425; WO 2012/106499; WO 2012/112743; WO 2012/125613, WO 2012/116440, WO 2011026240, WO 2013109521; US 8,883,840; or US 8,466,188, the entire contents of each application which are hereby incorporated by reference.

[00201] (38a) a Nav1.7 blocker such as (2-benzylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl)-(4-isopropoxy-3-methyl-phenyl)methanone, 2,2,2-trifluoro-1-[1′-[3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]-(4-isobutoxy-3-methoxy-phenyl)methanone, 1-(4-benzhydrylpiperazin-1-yl)-3-[2-(3,4-dimethylphenoxy)ethoxy]propan-2-

ol, (4-butoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]methanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]-(5-isopropoxy-6-methyl-2-pyridyl)methanone, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]methanone, 5-[2-methyl-4-[2-methyl-6-(2,2,2-trifluoroacetyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-carbonyl]phenyl]pyridine-2-carbonitrile, (4-isopropoxy-3-methyl-phenyl)-[6-(trifluoromethyl)spiro[3,4-dihydro-2H-pyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]methanone, 2,2,2-trifluoro-1-[1′-[3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1′-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-3,3-dimethyl-spiro[2,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1′-(5-isopentyloxypyridine-2-carbonyl)-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]ethanone, (4-isopropoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]methanone, 2,2,2-trifluoro-1-[1′-(5-isopentyloxypyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]ethanone, 1-[(3S)-2,3-dimethyl-1′-[4-(3,3,3-trifluoropropoxymethyl)benzoyl]spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]-2,2,2-trifluoro-ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]-[3-methoxy-4-[(1R)-1-methylpropoxy]phenyl]methanone, 2,2,2-trifluoro-1-[1′-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]ethanone, 1-[1′-[4-methoxy-3-(trifluoromethyl)benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-6-yl]-2,2-dimethyl-propan-1-one, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]methanone, [2-methyl-6-(1-methylcyclopropanecarbonyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]-[4-(3,3,3-trifluoropropoxymethyl)phenyl]methanone, 4-bromo-N-(4-bromophenyl)-3-[(1-methyl-2-oxo-4-piperidyl)sulfamoyl]benzamide or (3-chloro-4-isopropoxy-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4′-piperidine]-1′-yl]methanone.

[00202] (39) a Nav1.8 blocker, such as PF-04531083, PF-06372865 and such as those disclosed in International Patent Application Publication Nos. WO 2008/135826;

WO 2006/011050; WO 2013/061205; WO 2013131018; WO 2013114250; WO 2014/1280808; WO 2014/120815; and WO 2014/120820; U.S. Patent Application Publication No. US 2013/0303535; and U.S. Patent No. 8,466,188, the entire contents of each which are hereby incorporated by reference.

[00203] (39a) a Nav1.8 blocker such as 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-((5-fluoro-2-hydroxybenzyl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(o-tolyloxy)-5-(trifluoromethyl)benzamide, 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, In one embodiment, the compound is 3-(4-fluoro-2-methoxyphenoxy)-N-(3-(methylsulfonyl)phenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid, 2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide,

3-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)quinoline-3-carboxamide, N-(3-sulfamoylphenyl)-3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamide, 3-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 5-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid, 3-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)quinoxaline-2-carboxamide, 3-(4-fluoro-2-methoxyphenoxy)-N-(pyridin-4-yl)quinoxaline-2-carboxamide, 3-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, N-(3-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, N-(4-carbamoylphenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)benzoic acid, N-(4-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 5-(2-(2,4-dimethoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)benzoic acid, 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 4-(2-(2-chloro-4-fluorophenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-chloro-2-methylphenoxy)benzamido)benzoic acid, 5-(4-(tert-butyl)-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-dimethoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(2-chloro-4-fluorophenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-difluorophenoxy)benzamido)picolinic acid, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-

(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluorophenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-chloro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide or N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide.

[00204] (40) a combined Nav1.7 and Nav1.8 blocker, such as DSP-2230 or BL-1021;

[00205] (41) a 5-HT3 antagonist, such as ondansetron;

[00206] (42) a TPRV 1 receptor agonist, such as capsaicin (NeurogesX®, Qutenza®); and the pharmaceutically acceptable salts and solvates thereof;

[00207] (43) a nicotinic receptor antagonist, such as varenicline;

[00208] (44) an N-type calcium channel antagonist, such as Z-160;

[00209] (45) a nerve growth factor antagonist, such as tanezumab;

[00210] (46) an endopeptidase stimulant, such as senrebotase;

[00211] (47) an angiotensin II antagonist, such as EMA-401;

[00212] In one embodiment, the additional appropriate therapeutic agents are selected from V-116517, Pregbalin, controlled release Pregbalin, Ezogabine (Potiga®), Ketamine/amitriptyline topical cream (Amiket®), AVP-923, Perampanel (E-2007), Ralfinamide, transdermal bupivacaine (Eladur®), CNV1014802, JNJ-10234094 (Carisbamate), BMS-954561 or ARC-4558.

[00213] In another embodiment, the additional appropriate therapeutic agents are selected from N-(6-amino-5-(2,3,5-trichlorophenyl)pyridin-2-yl)acetamide; N-(6-amino-5-(2-chloro-5-methoxyphenyl)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxamide; or 3-((4-(4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)methyl)oxetan-3-amine.

[00214] In another embodiment, additional appropriate therapeutic agents are selected from the following:

[00215] (1) an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine, or difelikefalin;

[00216] (2) a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen (including without limitation intravenous ibuprofen (e.g., Caldolor®)), indomethacin, ketoprofen, ketorolac (including without limitation ketorolac tromethamine (e.g., Toradol®)), meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;

[00217] (3) a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, thiamylal or thiopental;

[00218] (4) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;

[00219] (5) a histamine (H_1) antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;

[00220] (6) a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;

[00221] (7) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine;

[00222] (8) an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2- piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (-)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-l- piperidinyl]-l-hydroxyethyl-3,4-dihydro-2(lH)-quinolinone;

[00223] (9) an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmedetomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-l, 2,3,4-tetrahydroisoquinolin-2-yl)-5-(2-pyridyl) quinazoline;

[00224] (10) a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;

[00225] (11) an anticonvulsant, e.g. carbamazepine (Tegretol®), lamotrigine, topiramate, lacosamide (Vimpat®) or valproate;

[00226] (12) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11 -tetrahydro-9-methyl-5-(4- methylphenyl)-7H-[l,4]diazocino[2,l-g][l,7]-naphthyridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(lR)-l-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-l,2-dihydro-3H-l,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

[00227] (13) a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;

[00228] (14) a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;

[00229] (15) a coal-tar analgesic, in particular paracetamol;

[00230] (16) a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone,

perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;

[00231] (17) a vanilloid receptor agonist (e.g. resinferatoxin or civamide) or antagonist (e.g. capsazepine, GRC-15300);

[00232] (18) a beta-adrenergic such as propranolol;

[00233] (19) a local anesthetic such as mexiletine;

[00234] (20) a corticosteroid such as dexamethasone;

[00235] (21) a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;

[00236] (22) a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-l-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);

[00237] (23) a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-l-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

[00238] (24) Tramadol®, Tramadol ER (Ultram ER®), Tapentadol ER (Nucynta®);

[00239] (25) a PDE5 inhibitor, such as 5-[2-ethoxy-5-(4-methyl-l-piperazinyl-sulphonyl)phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)- 2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',l':6,l]-pyrido[3,4-b]indole-l,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-l-yl-l-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,l-f][l,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(l-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(l-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-l-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H- pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-l-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(l- methyl-7-oxo-3-propyl-6,7-dihydro-lH-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(l-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

[00240] (26) an alpha-2-delta ligand such as gabapentin (Neurontin®), gabapentin GR (Gralise®), gabapentin, enacarbil (Horizant®), pregabalin (Lyrica®), 3-methyl gabapentin, (l[alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-

aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(lR,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(l-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(l-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;

[00241] (27) a cannabinoid such as KHK-6188;

[00242] (28) metabotropic glutamate subtype 1 receptor (mGluRl) antagonist;

[00243] (29) a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, ericlamine and trazodone;

[00244] (30) a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;

[00245] (31) a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine (Cymbalta®), milnacipran and imipramine;

[00246] (32) an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(l-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(l-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(l-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(l-iminoethyl)amino]-5-heptenoic acid, 2-[[(lR,3S)-3-amino-4-hydroxy-l-(5-thiazolyl)-butyl]thio]-S-chloro-S-pyridinecarbonitrile; 2-[[(lR,3S)-3-amino-4-hydroxy-l-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[(lR,3S)-3-amino-4-hydroxy-l-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[(lR,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-

chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, NXN-462, or guanidinoethyldisulfide;

[00247] (33) an acetylcholinesterase inhibitor such as donepezil;

[00248] (34) a prostaglandin E2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6- dimethyl-lH-imidazo[4,5-c]pyridin-l-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(15)-l-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;

[00249] (35) a leukotriene B4 antagonist; such as l-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP- 105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870;

[00250] (36) a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6- tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-l-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl)-l,4-benzoquinone (CV-6504);

[00251] (37) a sodium channel blocker, such as lidocaine, lidocaine plus tetracaine cream (ZRS-201) or eslicarbazepine acetate;

[00252] (38) a Nav1.7 blocker, such as XEN-402, XEN403, TV-45070, PF-05089771, CNV1014802, GDC-0276, RG7893 BIIB-074, BIIB-095, ASP-1807, DSP-3905, OLP-1002, RQ-00432979, FX-301, DWP 1706, DWP-17061, IMB-110, IMB-111, IMB-112 and such as those disclosed in WO2011/140425 (US2011/306607); WO2012/106499 (US2012196869); WO2012/112743 (US2012245136); WO2012/125613 (US2012264749), WO2012/116440 (US2014187533), WO2011026240 (US2012220605), US8883840, US8466188, or WO2013/109521 (US2015005304), the entire contents of each application hereby incorporated by reference.

[00253] (38a) a Nav1.7 blocker such as (2-benzylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl)-(4-isopropoxy-3-methyl-phenyl)methanone, 2,2,2-trifluoro-1-[1'-[3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(4-isobutoxy-3-methoxy-phenyl)methanone, 1-(4-benzhydrylpiperazin-1-yl)-3-[2-(3,4-dimethylphenoxy)ethoxy]propan-2-ol, (4-butoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-

dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(5-isopropoxy-6-methyl-2-pyridyl)methanone, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 5-[2-methyl-4-[2-methyl-6-(2,2,2-trifluoroacetyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carbonyl]phenyl]pyridine-2-carbonitrile, (4-isopropoxy-3-methyl-phenyl)-[6-(trifluoromethyl)spiro[3,4-dihydro-2H-pyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-[3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-3,3-dimethyl-spiro[2,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopentyloxypyridine-2-carbonyl)-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, (4-isopropoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopentyloxypyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[(3S)-2,3-dimethyl-1'-[4-(3,3,3-trifluoropropoxymethyl)benzoyl]spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2,2-trifluoro-ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[3-methoxy-4-[(1R)-1-methylpropoxy]phenyl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[1'-[4-methoxy-3-(trifluoromethyl)benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2-dimethyl-propan-1-one, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [2-methyl-6-(1-methylcyclopropanecarbonyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[4-(3,3,3-trifluoropropoxymethyl)phenyl]methanone, 4-bromo-N-(4-bromophenyl)-3-[(1-methyl-2-oxo-4-piperidyl)sulfamoyl]benzamide or (3-chloro-4-isopropoxy-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone.

[00254] (39) a Nav1.8 blocker, such as PF-04531083, PF-06372865 and such as those disclosed in WO2008/135826 (US2009048306), WO2006/011050 (US2008312235), WO2013/061205 (US2014296313), US20130303535, WO2013131018, US8466188, WO2013114250 (US2013274243), WO2014/120808 (US2014213616), WO2014/120815

(US2014228371) WO2014/120820 (US2014221435), WO2015/010065 (US20160152561), WO2015/089361 (US20150166589), WO2019014352 (US20190016671), WO2020/014243 and WO2020/014246 the entire contents of each application hereby incorporated by reference.

[00255] (39a) a Nav1.8 blocker such as 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-((5-fluoro-2-hydroxybenzyl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(o-tolyloxy)-5-(trifluoromethyl)benzamide, 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 2-(4-fluoro-2-methyl-phenoxy)-N-(2-oxo-1H-pyridin-4-yl)-4-(trifluoromethyl)benzamide, [4-[[2-(4-fluoro-2-methyl-phenoxy)-4-(trifluoromethyl)benzoyl]amino]-2-oxo-1-pyridyl]methyl dihydrogen phosphate, 3-(4-fluoro-2-methoxyphenoxy)-N-(3-(methylsulfonyl)phenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid, 2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-

sulfamoylphenyl)quinoline-3-carboxamide, 3-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)quinoline-3-carboxamide, N-(3-sulfamoylphenyl)-3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamide, 3-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 5-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid, 3-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)quinoxaline-2-carboxamide, 3-(4-fluoro-2-methoxyphenoxy)-N-(pyridin-4-yl)quinoxaline-2-carboxamide, 3-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, N-(3-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, N-(4-carbamoylphenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)benzoic acid, N-(4-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 5-(2-(2,4-dimethoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)benzoic acid, 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 4-(2-(2-chloro-4-fluorophenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-chloro-2-methylphenoxy)benzamido)benzoic acid, 5-(4-(tert-butyl)-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-dimethoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(2-chloro-4-fluorophenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-

difluorophenoxy)benzamido)picolinic acid, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluorophenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-chloro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide, N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethoxy)benzamide, 4-[[2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, 4-[[3-chloro-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, 4-[[2-fluoro-6-[2-

(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-3-(difluoromethyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethoxy)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-6-[2-chloro-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-methyl-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2,3,4-trifluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzamide, N-(2-carbamoyl-4-pyridyl)-3-fluoro-5-[2-methoxy-4-(trifluoromethoxy)phenoxy]-2-(trifluoromethyl)pyridine-4-carboxamide, 4-[[6-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-6-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(4-carbamoyl-3-fluoro-phenyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-4-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[3-fluoro-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-[2-methoxy-4-(trifluoromethoxy)phenoxy]-5-(1,1,2,2,2-pentafluoroethyl)benzamide, 4-[[4-(difluoromethoxy)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-fluoro-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, 4-[[4-cyclopropyl-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-5-fluoro-2-[2-methoxy-4-(trifluoromethoxy)phenoxy]-4-(trifluoromethyl)benzamide, 5-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-(4-fluorophenoxy)-3-(trifluoromethyl)benzamide, or 4-[[2-fluoro-6-[3-fluoro-2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide.

[00256] (40) a combined Nav1.7 and Nav1.8 blocker, such as DSP-2230, Lohocla201 or BL-1021;

[00257] (41) a 5-HT3 antagonist, such as ondansetron;

[00258] (42) a TPRV 1 receptor agonist, such as capsaicin (NeurogesX®, Qutenza®); and the pharmaceutically acceptable salts and solvates thereof;

[00259] (43) a nicotinic receptor antagonist, such as varenicline;

[00260] (44) an N-type calcium channel antagonist, such as Z-160;

[00261] (45) a nerve growth factor antagonist, such as tanezumab;

[00262] (46) an endopeptidase stimulant, such as senrebotase;

[00263] (47) an angiotensin II antagonist, such as EMA-401;

[00264] (48) acetaminophen (including without limitation intravenous acetaminophen (e.g., Ofirmev®));

[00265] (49) bupivacaine (including without limitation bupivacaine liposome injectable suspension (e.g., Exparel®) bupivacaine ER (Posimir), bupivacaine collagen (Xaracoll) and transdermal bupivacaine (Eladur®)); and

[00266] (50) bupivacaine and meloxicam combination (e.g., HTX-011).

[00267] In one embodiment, the additional appropriate therapeutic agents are selected from XEN907, NW3509, GTX analogs, ASP 1807, OLP 1002, ST-2427, V-116517, Pregabalin, controlled release Pregabalin, Ezogabine (Potiga®). Ketamine/amitriptyline topical cream (Amiket®), AVP-923, Perampanel (E-2007), Ralfinamide, transdermal bupivacaine (Eladur®), CNV1014802, JNJ-10234094 (Carisbamate), BMS-954561 or ARC-4558.

[00268] In another embodiment, the additional appropriate therapeutic agents are selected from N-(6-amino-5-(2,3,5-trichlorophenyl)pyridin-2-yl)acetamide; N-(6-amino-5-(2-chloro-5-methoxyphenyl)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxamide; or 3-((4-(4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)methyl)oxetan-3-amine.

[00269] In another embodiment, the additional therapeutic agent is selected from a GlyT2/5HT2 inhibitor, such as Operanserin (VVZ149), a TRPV modulator such as CA008, CMX-020, NEO6860, FTABS, CNTX4975, MCP101, MDR16523, or MDR652, a EGR1 inhibitor such as Brivoglide (AYX1), an NGF inhibitor such as Tanezumab, Fasinumab, ASP6294, MEDI7352, a Mu opioid agonist such as Cebranopadol, Apadaz, NKTR181 (oxycodegol), a CB-1 agonist such as NEO1940 (AZN1940), an imidazoline 12 agonist such as CR4056 or a p75NTR-Fc modulator such as LEVI-04.

[00270] In another embodiment, the additional therapeutic agent is oliceridine or ropivacaine (TLC590).

[00271] In another embodiment, the additional therapeutic agent is a sodium channel inhibitor (also known as a sodium channel blocker), such as the Nav1.7 and Nav1.8 blockers identified above.

[00272] The amount of additional therapeutic agent present in the compositions described herein will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions will range from about 10% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00273] Another embodiment described herein comprises a method of inhibiting a voltage-gated sodium channel in a subject comprising administering to the subject Compound 1 or a composition thereof. In one aspect, the voltage-gated sodium channel is Nav1.8.

[00274] Another embodiment described herein comprises a method of inhibiting a voltage-gated sodium channel in a biological sample comprising contacting the biological sample with an effective amount of Compound 1 or a composition thereof. In one aspect, the voltage-gated sodium channel is Nav1.8. The term "biological sample," as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00275] Inhibition of Nav1.8 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium channels in biological and pathological phenomena; and the comparative evaluation of new sodium channel inhibitors. Without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of Nav1.8 is implicated in the disease, condition, or disorder. When activation or hyperactivity of Nav1.8 is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a "Nav1.8 -mediated disease, condition, or disorder." Another embodiment described herein comprises a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of Nav1.8 is implicated in the disease state.

[00276] The activity of a compound described herein as an inhibitor of Nav1.8 may be assayed according to methods described in U.S. Patent No. 9,163,042 which is incorporated herein by reference for the teachings thereof, or according to methods available to one of ordinary skill in the art.

[00277] It will be readily apparent to one of ordinary skill in the relevant arts that suitable modifications and adaptations to the compositions, formulations, methods, and applications described herein can be made without departing from the scope of any embodiments or aspects thereof. The compositions and methods provided are exemplary and are not intended to limit the scope of any of the specified embodiments. All of the various embodiments, aspects, and options disclosed herein can be combined in any variations or iterations. The scope of the compositions, formulations, processes, and methods described herein include all actual or potential combinations of embodiments, aspects, options, examples, and preferences herein described. Compositions and formulations described herein may omit any component on include any component disclosed elsewhere herein. The ratios of the mass of any component of any of the formulations disclosed herein to the mass of any other component in the formulation or to the total mass of the other components in the formulation are hereby disclosed as if they were expressly disclosed. Should the meaning of the terms in any of the patents or publications incorporated by reference conflict with the meaning of the terms used in this disclosure, the meaning of the terms in this disclosure are intended to be controlling. Furthermore, the foregoing discussion discloses and describes exemplary embodiments. All patents and publications cited herein are incorporated by reference herein for the relevant specific teachings thereof.

EXAMPLES

Example 1

[00278] A synthesis method for (4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2*H*)-yl)methyl dihydrogen phosphate (Compound 1) is described in Examples 6, 13–15, and 15A–15F (col. 60, line 41–col. 61, line 16; col. 65, line 36–col. 75, line 12) of U.S. Patent No. 9,163,042, which is incorporated herein by reference for the teachings thereof.

[00279] Form B of Compound 1, including the preparation and characterization thereof, is also described in U.S. Patent No. 9,163,042, col. 20, line 47–col. 25, line 53; col. 26, lines 39–51; and Figures 2–4, which are incorporated herein by reference for the teachings thereof.

Example 1A

Jet-Milling

[00280] Particle size reduction by jet-milling was achieved by the two following procedures.

[00281] In one procedure, jet-milling was achieved using a Jet-O-Mizer instrument by first passing Compound 1 Form B (300g) through a 20-mesh sieve and collecting the sieved material. The Jet-O-Mizer parameters (air supply = 100 psi, grinding nozzle = 60 psi and pusher nozzle = 80psi) were then set before passing the sieved material through the mill and collecting the milled material (282 g, milling efficiency of 91%).

[00282] In another procedure, particle size reduction of Form B was achieved using a fluid energy jet mill (8" pancake mill manufactured by CMD). The material to be micronized entered the mill at the material inlet via a separate feed system which metered the feed rate. The material then passed through a venturi charged by compressed air or nitrogen (feed gas) where it was accelerated into the grinding chamber. In the grinding chamber, a separate supply of compressed air or nitrogen (grinding gas) was distributed through precisely aligned jets which created a vortex accelerating the material tangentially and radially inward. Oversized particles were acted on by centrifugal force moving them from the inlet towards the outer periphery of the air flow path where they impacted against particles already in the vortex. This particle-on-particle impact caused size reduction. As particles became smaller in size, they moved toward the center of the mill and exited at the product outlet for collection. In-process samples of the micronized drug substance were

collected for particle size analysis. Based upon the particle size results, the milling parameters were adjusted to achieve the required particle size specification. A scanning electron microscope (SEM) image of the jet-milled material is provided in Figure 7. The image was acquired on a Quanta Scanning Electron Microscope (FEI/Thermo Fisher Scientific) with a field emission gun (FEG) as the electron beam source and an Everhart-Thornley Detector (ETD) as a secondary electron and back-scattered electron detector. The electron beam was accelerated through a voltage gap of 7.5 kV for imaging. Sample powders were mounted onto an aluminum SEM stub using double sided carbon tape and then sputter coated on a Denton Vacuum system (gold target, 60% setpoint, 60 s) before imaging.

Example 2

[00283] X-Ray Powder Diffraction

[00284] X-ray powder diffraction (XRPD) spectra were recorded at room temperature in reflection mode using a PANalytical Empyrean system equipped with a sealed tube source and a PIXcel 1D Medipix-2 detector (Malvern PANalytical Inc, Westborough, Massachusetts). The X-Ray generator operated at a voltage of 45 kV and a current of 40 mA with copper radiation (1.54060 Å). The sample was placed in a back filled sample holder and loaded into the instrument. The sample was scanned over the range of about 3° to about 40° 2θ with a step size of 0.0131303° and 49.725s per step. A sample of jet-milled, crystalline Form B of Compound 1 was subjected to XRPD under the conditions described above. The salient peaks are shown in Table 2 and the spectrum is shown in Figure 2.

Table 2. X-ray Powder Diffraction of Micronized Crystalline Form B of Compound 1

Peak Position (°2θ)	Full width at half maximum, left (°2θ)	Area (counts·°2θ)	Relative Intensity (%)
15.12	0.14	1596.58	62.49
16.35	0.13	766.65	33.01
17.72	0.12	474.35	22.69
18.00	0.15	863.00	30.96
19.24	0.13	1562.28	67.26
19.75	0.14	1019.14	39.89
20.12	0.09	515.76	31.72
20.43	0.17	1959.70	64.90
20.88	0.19	1593.55	45.74
22.09	0.17	2376.45	78.70

23.40	0.20	3716.46	100.00
24.20	0.19	1759.51	50.50
24.61	0.12	720.55	34.47
24.96	0.10	465.87	25.07
26.22	0.15	2003.51	71.88
29.45	0.23	1777.73	42.52
29.90	0.20	2121.14	57.07

Example 3

[00285] Differential Scanning Calorimetry (DSC)

[00286] DSC data were acquired using a TA Instruments Q2000. A sample with a weight between 1 and 10 mg was weighed into an aluminum pan. This pan was placed in the sample position in the calorimeter cell. An empty pan was placed in the reference position. The calorimeter cell was closed and a flow of nitrogen was passed through the cell. The heating program was set to heat the sample at a heating rate of 10 °C/min to a temperature of 200–350 °C. When the run was completed, the data were analyzed using the DSC analysis program in the system software.

[00287] A sample of jet-milled, crystalline Form B of Compound 1 was subject to DSC under the conditions described above. The thermogram is shown in Figure 3.

Example 4A

[00288] Capsule Dosage Form of Compound 1

[00289] Capsules were manufactured at a dose strength of 250 mg of Compound 1 wherein tocopherol polyethylene glycol succinate (TPGS) was melted overnight at 50 ± 5 °C in an oven. The melted TPGS and Form B of Compound 1 were added to a Skerman mixer to form a suspension. Once a homogeneous dispersion was formed, it was held at 50 ± 5 °C and filled in hydroxypropyl methylcellulose Vcaps® 00EL capsules (Capsugel) using a Bosch 1500L automatic capsule filling machine. Each capsule contained 250 mg of Compound 1 and 750 mg of TPGS.

Example 4B

[00290] Capsule Dosage Form of Compound 1

[00291] Capsules were manufactured at a dose strength of 250 mg of Compound 1. The capsule fill was prepared by melting tocopherol polyethylene glycol succinate (TPGS) overnight

at 65 ± 5 °C in an oven. The melted TPGS and micronized Compound 1, Form B, were added to a Skerman mixer, and combined to form a suspension. Once a homogeneous dispersion was formed, it was held at 65 ± 5 °C and used to fill hydroxypropyl methylcellulose (hypromellose) Vcaps® size 0 capsules (Capsugel) using a Bosch 1500L automatic capsule filling machine. Each capsule contained 250 mg of Compound 1 and 375 mg of TPGS as shown in Table 3.

Table 3: Capsule Dosage Form

Component	Mass (mg)	Weight Percent (%)
Micronized Compound 1, Form B	250	40
TPGS	375	60
Total	625	100

Example 5

[00292] A sample of the fill composition used in the Capsule Dosage Form described in Example 4B was subject to XRPD under the conditions described above. The salient peaks are shown in Table 4 and the spectra is shown in Figure 4.

Table 4. X-ray Powder Diffraction of Compound 1

Peak Position (°2θ)	Full width at half maximum, left (°2θ)	Area (counts·°2θ)	Relative Intensity (%)
16.51	0.14	848.50	14.73
19.15	0.22	2275.28	25.56
20.27	0.12	743.15	15.77
20.58	0.13	664.38	12.69
21.04	0.15	1161.77	18.49
22.26	0.15	6282.53	100.00
23.55	0.12	2172.16	46.10
24.29	0.14	1252.09	21.74
24.87	0.18	1138.46	15.53
26.40	0.14	1318.47	22.89
26.76	0.15	644.26	10.25
29.61	0.10	539.63	12.88
30.06	0.12	771.91	16.38
31.27	0.14	613.39	10.65

Example 6

[00293] A sample of the fill composition used in the Capsule Dosage Form described in Example 4B was subject to DSC under the conditions described above. The thermogram is shown in Figure 5.

Example 7

[00294] Dissolution Experiments

[00295] Dissolution experiments were performed to evaluate the dissolution of the Compound 1 dosage forms. The method for determining the release of Compound 1 from the 250 mg capsule formulation described in Example 4B uses U.S.P. Apparatus 2, paddle speed of 75 rpm, and a medium of 0.5% Tween® 20 (polyoxyethylene sorbitan monolaurate 20) in 50 mM sodium acetate buffer (pH 4.5) at 37 °C using sinkers. General dissolution methods are described in the United States Pharmacopeia Convention ⟨711⟩ Dissolution (2011), which is incorporated by reference herein for such teachings. Samples were removed during dissolution at 5, 10, 15, 20, 30, 45, 60, and 75 minute time points while the paddle speed was increased to ≥200 rpm to homogenize the solution. The samples were filtered through 10 μm PVDF filters and were analyzed by HPLC. Experimental data are shown in Figure 6.

[00296] The capsule dosage forms comprising 250 mg of Compound 1 in 375 mg of tocopherol polyethylene glycol succinate (TPGS) had approximately 50% dissolution after ≤25 min (i.e., ~22 min). Disintegration of the capsule in this media has a slow, erosion-like mechanism owing to the quantity of TPGS in the formulations, which has a melting point at ≥40 °C. The capsules had approximately 90% dissolution after 30 min under the same conditions. The capsules fully dissolved within about 45 min under the same conditions.

Example 8

[00297] Clinical Trials

[00298] A randomized, open label crossover study with three treatment periods will be used to evaluate the bioavailability, pharmacokinetics, and food effects of Compound 1 in healthy adults. Sixty healthy, adult male and non-pregnant female subjects will be enrolled for each study. Subjects will be randomized to one of three treatment sequences prior to the first dose. The study will evaluate doses of Compound 1 (250 mg to 750 mg and 1500 mg, administered as 250 mg

capsule dosage forms). A single test dose of Compound 1 will be administered to the test subject on days 1, 8, and 15 with a 7-day washout period between each dosing (e.g., days 1–7 and 8–15). Blood samples will be drawn from the test subjects prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 120 hours post-dose. Blood samples will be analyzed for the concentrations of Compound 1, Compound 2, and metabolites of Compound 2.

Example 9

[00299] A randomized, crossover, open-label study with 3 treatment periods to evaluate test formulations of Compound 1 was conducted in human subjects. The study utilized 2 cohorts to evaluate the pharmacokinetics, relative bioavailability, and effects of food following a single administration of a Compound 1 test and reference formulations at a low dose (Cohort 1) and a high dose (Cohort 2). The low dose cohort (Cohort 1) received a 500 mg dose, while the high dose cohort (Cohort 2) received a 1500 mg dose.

[00300] The Compound 1 test formulation was a 250 mg Capsule, which was prepared as described in Example 4B. The test capsules were administered orally as a single dose of 500 mg (2 capsules; Cohort 1) or 1500 mg (6 capsules; Cohort 2) under fasted or fed conditions.

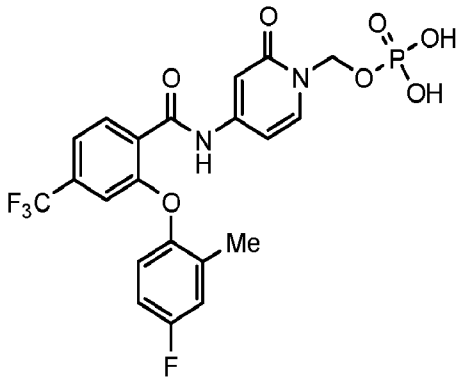
[00301] The Compound 1 reference formulation was a 250 mg Capsule, which was prepared as described in Example 4A. The reference capsules were administered orally as a single dose of 500 mg (2 capsules; Cohort 1) or 1500 mg (6 capsules; Cohort 2) under fasted conditions.

[00302] Plasma pharmacokinetic parameters were calculated using noncompartmental methods.

CLAIMS

What is claimed:

1. A pharmaceutical composition comprising a capsule fill of Compound 1



(I),

or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable suspension agents.

2. The pharmaceutical composition of claim 1, comprising a capsule fill of Compound 1 and one or more pharmaceutically acceptable suspension agents.

3. The composition of claim 2, wherein the Compound 1 is crystalline Form B.

4. The composition of any one of claims 1-3, wherein the Compound 1 is micronized.

5. The composition any one of claims 1–4, wherein the composition comprises about 30% to about 50% of Compound 1 and about 50% to about 70% of one or more pharmaceutically acceptable suspension agents.

6. The composition any one of claims 1–5, wherein the composition comprises about 40% of Compound 1 and about 60% of one or more pharmaceutically acceptable suspension agents.

7. The composition of any one of claims 1–6, wherein the composition comprises about 200–300 mg of Compound 1 and 300–450 mg of the one or more pharmaceutically acceptable suspension agents.

8. The composition of any one of claims 1–7, wherein the composition comprises about 250 mg of Compound 1 and 375 mg of the one or more pharmaceutically acceptable suspension agents.

9. The composition of any one of claims 1–8, wherein the pharmaceutically acceptable suspension agent comprises one or more of tocopherol polyethylene glycol succinate (TPGS), lauroyl polyoxyl-32 glycerides, stearoyl polyoxyl-32 glycerides or polyethylene glycol monostearate.

10. The composition of any one of claims 1–9, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm.

11. The composition of any one of claims 1–10, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$ of about ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2 μm.

12. The composition of any one of claims 1–11, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 2.5 μm.

13. The composition of any one of claims 1–12, wherein the composition comprises:
    (a) about 30–50% by weight of Compound 1; and
    (b) about 50–70% by weight of TPGS.

14. The composition of any one of claims 1–13, wherein the composition comprises:
    (a) about 40% by weight of Compound 1; and
    (b) about 60% by weight of TPGS.

15. The composition of any one of claims 1–14, wherein the composition comprises a hard capsule dosage form encapsulating the composition.

16. The composition of any one of claims 1–15, wherein the composition is effective at treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

17. A method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof comprising administering an effective amount of the composition of any one of claims 1–16.

18. An oral pharmaceutical dosage form comprising a capsule encapsulating a matrix fill comprising:
    (a) 20–80% by weight of the fill composition of Compound 1, or a pharmaceutically acceptable salt thereof; and
    (b) 20–80% by weight of the fill composition of one or more suspension agents.

19. The dosage form of claim 18, wherein the matrix fill comprises:
    (a) 20–80% by weight of the fill composition of Compound 1; and
    (b) 20–80% by weight of the fill composition of one or more suspension agents.

20. The dosage form of claim 19, wherein the Compound 1 is crystalline Form B.

21. The dosage form of any of claims 18 -20, wherein the Compound 1 is micronized.

22. The dosage form of any one of claims 18–21, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm.

23. The dosage form of any one of claims 18–22, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$ of about ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2.0 μm.

24. The dosage form of any one of claims 18–23, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$ of about 2.5 μm.

25. The dosage form of any one of claims 18–24, wherein the suspension agent comprises one or more of tocopherol polyethylene glycol succinate (TPGS), lauroyl polyoxyl-32 glycerides, stearoyl polyoxyl-32 glycerides, polyethylene glycol monostearate, polyethylene glycols of molecular weight ranging from about 200 to about 8000 (M_N, number average molecular weight), polyvinylpyrrolidone, propylene glycol, or combinations thereof.

26. The dosage form of form of any one of claims 18–25, wherein the dosage form comprises:
    (a) about 20% to about 50% by weight of Compound 1; and
    (b) about 50% to about 80% by weight of one or more suspension agents.

27. The dosage form of any one of claims 18–26, wherein the dosage form comprises:
    (a) about 30% to about 40% by weight of Compound 1; and
    (b) about 60% to about 70% by weight of one or more suspension agents.

28. The dosage form of any one of claims 18–27, wherein the dosage form comprises:
    (a) about 40% by weight of Compound 1; and
    (b) about 60% by weight of one or more suspension agents.

29. The dosage form of any one of claims 18–28, wherein the suspension agent comprises tocopherol polyethylene glycol succinate (TPGS).

30. The dosage form of any one of claims 18–29, wherein the dosage form comprises:
    (a) about 40% by weight of Compound 1; and
    (b) about 60% by weight of TPGS.

31. The dosage form of any one of claims 18–30, wherein the dosage form comprises about 50 mg to about 2000 mg of Compound 1 in each dosage form.

32. The dosage form of any one of claims 18–31, wherein the dosage form comprises about 50 mg, 100 mg, 150 mg, 250 mg, 300 mg, 500 mg, 750 mg, or 1000 mg of Compound 1 in each dosage form.

33. The dosage form of any one of claims 18–32, wherein the dosage form comprises about 250 mg to about 300 mg of Compound 1 in each dosage form.

34. The dosage form of any one of claims 18–33, wherein the dosage form comprises 250 mg of Compound 1 and 375 mg of TPGS.

35. The dosage form of any one of claims 18–34, wherein the capsule is a hydroxypropylmethylcellulose two-piece hard capsule.

36. The dosage form of any one of claims 18–35, wherein the dosage form is stable for at least 3 months when stored at a temperature up to 30 °C and a relative humidity up to 65%.

37. The dosage form of any one of claims 18–36, wherein about 50% of the dosage form dissolves within about 20 minutes at 37 °C and 75 rpm in a medium of 0.5% polysorbate monolaurate 20 (Tween® 20) in 50 mM sodium acetate buffer (pH 4.5) using a U.S.P. Apparatus 2.

38. The dosage form of any one of claims 18–37, wherein the composition is effective at inhibiting voltage gated sodium channel 1.8.

39. The dosage form of any one of claims 18–38, wherein the composition is effective at treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

40. Use of the dosage form of one of claims 18–38, wherein the composition is effective at treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

41. A method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof comprising administering an effective amount of the dosage form of any one of claims 18–39.

42. The method of claim 41, wherein the pain comprises one or more of abdominal pain, abnormal gastrointestinal motility pain, acute herpes zoster pain, acute inflammatory pain, acute intermittent pain, acute musculoskeletal pain, acute obstetric pain, acute pain, acute post-operative pain (e.g., bunionectomy pain; abdominoplasty pain; knee pain from a total knee replacement; hip pain from a total hip replacement; pain from a laminectomy; pain from a hernia repair; or hemorrhoid removal pain), acute tendonitis pain, acute visceral pain, adiposis dolorosa pain, amyotrophic lateral sclerosis pain, angina-induced pain, anti-retroviral therapy induced neuralgia, anxiety pain, appendicitis pain, arrhythmia pain, arthritis pain, ataxia pain, back pain, Behçet's disease pain, bipolar disorder pain, bladder and urogenital disease pain, bone pain, brachial plexus avulsion injury pain, breakthrough pain, burn pain, burning mouth syndrome pain, bursitis pain, cancer chemotherapy induced neuralgia, cancer pain, cardiac arrhythmia pain, cardiac pain, carpal tunnel syndrome pain, central pain, cerebral ischemia, Cesarean-section pain, Charcot-Marie Tooth neuropathic pain, chemotherapy induced neuropathic pain, chest pain, cholecystitis pain, chronic and acute headache pain, chronic and acute neuropathic pain, chronic arthritis, chronic pain, chronic visceral pain, cluster headache pain, cold pain, complex regional pain syndrome, Crohn's disease pain, dental pain (e.g., third molar extraction), depression pain, diabetic neuralgia, diabetic neuropathic pain, diabetic peripheral neuropathic pain, drug therapy induced neuralgia, ectopic proximal and distal discharge pain, endometriosis pain, epilepsy pain, erythromelalgia pain, exercise induced angina pain, exercise induced pain, exercise pain, Fabry's disease pain, femur cancer pain, fibromyalgia pain, general neuralgias, granuloma annulare pain, Guillain-Barre pain, gut pain, Haglund syndrome pain, head pain, headache pain, hereditary sensory neuropathic pain, hernia pain, herpetic neuralgia

pain, HIV-associated neuropathic pain, HIV-associated sensory neuropathic pain, hyperactivity bladder pain, hypertension pain, idiopathic pain, idiopathic sensory neuropathic pain, idiopathic small-fiber neuropathic pain, incontinence pain, inflammatory bowel disease pain, inflammatory pain, injury pain, interstitial cystitis (IC) pain, intestinal obstruction pain, intractable pain, irritable bowel syndrome pain, joint pain, labor pain, leprosy pain, lipoidica pain, malignancy pain, mechanical low back pain, migraine pain, Morton's neuroma pain, movement disorder pain, multiple sclerosis (MS) pain, musculoskeletal pain, myofascial pain syndrome pain, myotonia pain, neck pain, necrobiosis pain, nerve avulsion injury pain, nerve entrapment injury pain, neurodegenerative disorder pain, neuroendocrine disorder pain, neuropathic low back pain, neuropathic pain, nociceptive pain, non-malignant chronic bone pain, orofacial pain, osteoarthritis pain, painful bladder syndrome, painful legs, painful moving toes, painful neuromas, palpitations, pancreatic pain, paroxysmal extreme pain, pathological cough pain, pelvic pain, peripheral nerve injury pain, phantom pain, phlebitic pain, post spinal cord injury pain, post-amputation pain, post-herpetic neuralgia, post-mastectomy pain, post-stroke pain, postsurgical pain, premenstrual pain, prostatitis pain, pruritis pain, psychiatric disorder associated pain, pyelonephritis pain, radicular pain, radiculopathy, radiotherapy-induced neuropathic pain, renal colic pain, rheumatoid arthritis pain, sarcoidosis pain, sciatica pain, severe pain, shingles pain, sickle cell anemia pain, sinusitis pain, spinal cord injury pain, spinal stenosis pain, sports injury pain, stress-induced angina pain, stress-induced pain, stroke pain, temporomandibular joint pain, tendonitis pain, tension headache pain, thalamic pain, tinnitus pain, trauma pain, traumatic brain injury pain, traumatic neuroma, trigeminal autonomic cephalalgia, trigeminal neuralgia, urinary incontinence pain, visceral pain, widespread pain, or other types of pain.

43. The method of claim 41 or 42, wherein the pain comprises osteoarthritis pain.

44. The method of claim 41 or 42, wherein the pain comprises trigeminal neuralgia.

45. The method of claim 41 or 42, wherein the pain comprises herpetic neuralgia.

46. The method of claim 41 or 42, wherein the pain comprises chronic and acute neuropathic pain.

47. The method of claim 41 or 42, wherein the pain comprises bunionectomy pain.

48. The method of claim 41 or 42, wherein the pain comprises abdominoplasty pain.

49. The method of claim 41 or 42, wherein the pain comprises diabetic peripheral neuropathy.

50. The method of claim 41 or 42, wherein the pain comprises post-surgical pain from a total knee or total hip replacement or a laminectomy.

51. The method of claim 41 or 42, wherein the pain comprises chronic lower back pain.

52. The method of claim 41 or 42, wherein the pain comprises dental pain.

53. The method of claim 41 or 42, wherein the pain comprises post-surgical pain from a hernia repair or hemorrhoid removal.

54. The method of claim 41 or 42, wherein the pain comprises radiculopathy pain.

55. The method of any one of claims 17 and 41-54, wherein the total amount of TPGS administered to the subject is no more than about 4000 mg per day.

56. The method of any one of claims 17 and 41-55, wherein the subject limits consumption of dairy products for at least about 30 minutes prior to administration of the dosage form and for at least about 30 minutes after administration of the dosage form.

57. A method for manufacturing an oral pharmaceutical capsule dosage form comprising:

(a) melting one or more suspension agents at a temperature of about 40 °C to about 70 °C;

(b) combining Compound 1 with the melted suspension agent of (a) blending the combination, and maintaining the blend at a temperature of about 40 °C to about 70 °C; and

(c) encapsulating the blend in 2-piece hard capsules.

58. The method of claim 57, wherein the suspension agent comprises tocopherol polyethylene glycol succinate (TPGS).

59. The method of claim 57 or 58, wherein the temperature of (a) and (b) is about 65 °C.

60. The method of any one of claims 57–59, wherein the Compound 1 is crystalline Form B.

61. The method of any one of claims 57–60, wherein the Compound 1 is micronized to a median volume particle size, $D(v,0.5)$, of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm.

62. The method of any one of claims 57–61, wherein the Compound 1 is micronized to a median volume particle size, $D(v,0.5)$ of ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2 μm.

63. The method of any one of claims 57–62, wherein the Compound 1 is micronized by jet- or ball-milling.

64. An oral pharmaceutical capsule dosage form produced by the method of any one of claims 57–63.

65. The dosage form of claim 64, wherein the dosage form comprises:

(a) about 40% by weight Compound 1; and

(b) about 60% by weight of tocopherol polyethylene glycol succinate (TPGS).

66. The dosage form of 64 or 65, wherein the dosage form comprises:

(a) about 40% by weight of micronized crystalline Form B of Compound 1; and

(b) about 60% by weight of tocopherol polyethylene glycol succinate (TPGS).

67. The dosage form of any one of claims 64–66, wherein the dosage form comprises about 250 mg to about 300 mg of Compound 1.

68. The dosage form of any one of claims 64–67, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$, of about 1–10 μm, 1–5 μm, 1–3 μm, or 2–3 μm.

69. The dosage form of any one of claims 64–68, wherein the Compound 1 has a median volume particle size, $D(v,0.5)$, of about ≤ 10 μm, ≤ 5 μm, ≤ 4 μm, ≤ 3 μm, ≤ 2.5 μm, or ≤ 2 μm.

70. The dosage form of any one of claims 64–69, wherein the dosage form is effective at treating any type of pain in a subject in need thereof.

71. The dosage form of any one of claims 64–70, wherein the pain is osteoarthritis pain.

72. The dosage form of any one of claims 64-70, wherein the pain comprises trigeminal neuralgia.

73. The dosage form of any one of claims 64-70, wherein the pain comprises herpetic neuralgia.

74. The dosage form of any one of claims 64-70, wherein the pain comprises chronic and acute neuropathic pain.

75. The dosage form of any one of claims 64-70, wherein the pain comprises bunionectomy pain.

76. The dosage form of any one of claims 64-70, wherein the pain comprises abdominoplasty pain.

77. The dosage form of any one of claims 64-70, wherein the pain comprises diabetic peripheral neuropathy.

78. The dosage form of any one of claims 64-70, wherein the pain comprises osteoarthritis pain.

79. The dosage form of any one of claims 64-70, wherein the pain comprises post-surgical pain from a total knee or total hip replacement or a laminectomy.

80. The dosage form of any one of claims 64-70, wherein the pain comprises chronic lower back pain.

81. The dosage form of any one of claims 64-70, wherein the pain comprises dental pain.

82. The dosage form of any one of claims 64-70, wherein the pain comprises post-surgical pain from a hernia repair or hemorrhoid removal.

83. The dosage form of any one of claims 64-70, wherein the pain comprises radiculopathy pain.

84. Use of the dosage form of any one of claims 64-70 for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof.

85. A method for treating, amelioration of, reducing the symptoms of, prophylaxis of, or lessening the severity of any type of pain in a subject in need thereof comprising administering an effective amount of a pharmaceutical composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable suspension agents, wherein the total amount of the one or more suspension agents administered to the subject is no more than about 4000 mg per day.

86. The method of claim 85, wherein the total amount of the one or more suspension agents is about 100 mg to about 3500 mg per day.

87. The method of any one of claims 85-86, wherein the total amount of the one or more suspension agents is about 100 mg to about 3500 mg per day.

88. The method of any one of claims 85-87, wherein the total amount of the one or more suspension agents is about 250 mg to about 3450 mg per day.

89. The method of any one of claims 85-88, wherein the total amount of the one or more suspension agents is about 500 mg to about 3425 mg per day.

90. The method of any one of claims 85-89, wherein the total amount of the one or more suspension agents is about 750 mg to about 3400 mg per day.

91. The method of any one of claims 85-90, wherein the total amount of the one or more suspension agents is about 1000 mg to about 3375 mg per day.

92. The method of any one of claims 85-91, wherein the one or more suspension agents consists of TPGS.

93. The method of any one of claims 17, 41-56, and 85-92, wherein the subject is a human.

94. The dosage form of any one of claims 39 and 70-83, wherein the subject is a human.

95. The use of any one of claims 40 and 84, wherein the subject is a human.

FIG. 1

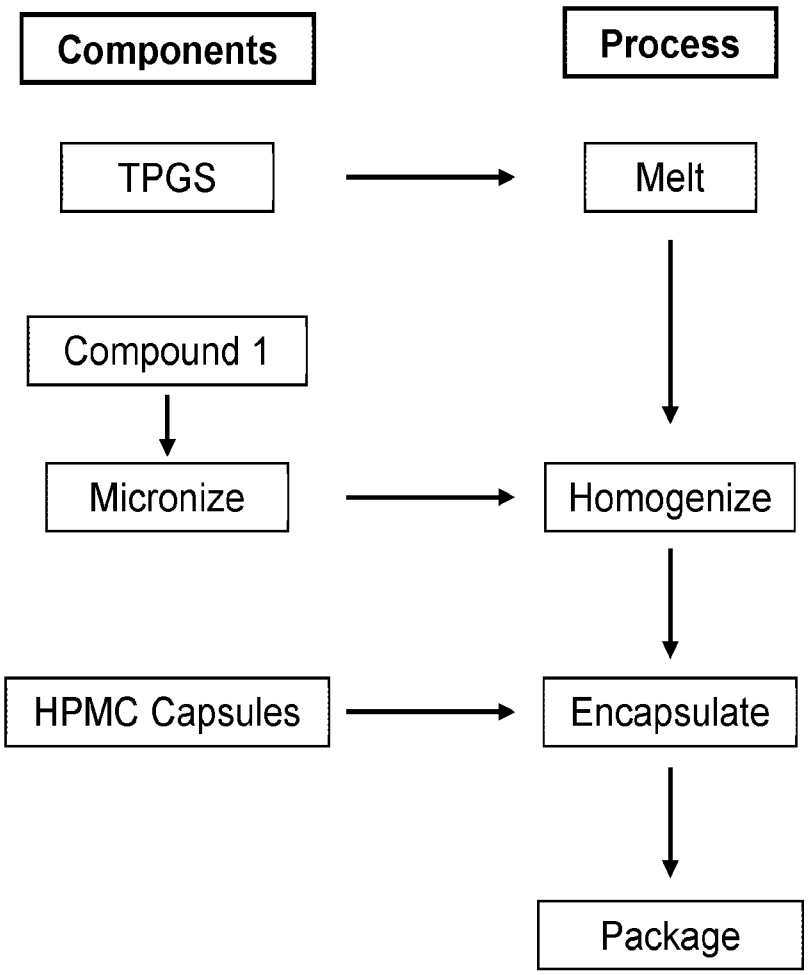

Components
Process
TPGS
Melt
Compound 1
Micronize
Homogenize
HPMC Capsules
Encapsulate
Package

FIG. 2

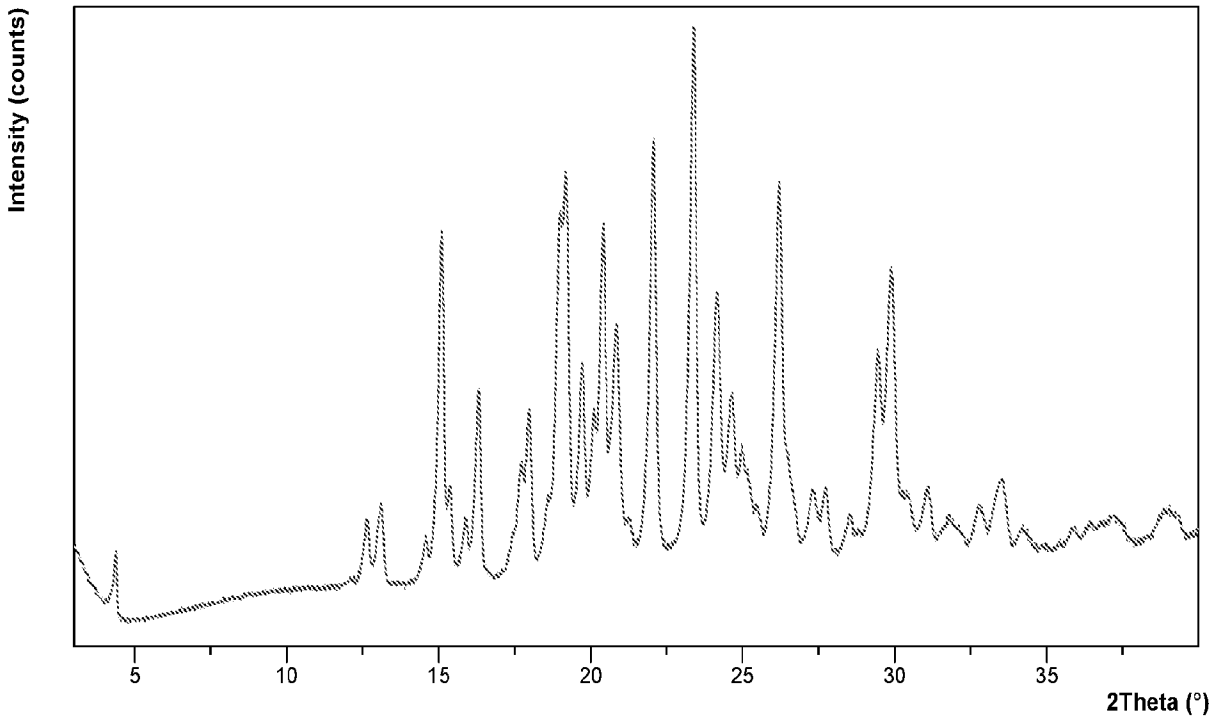


FIG. 3

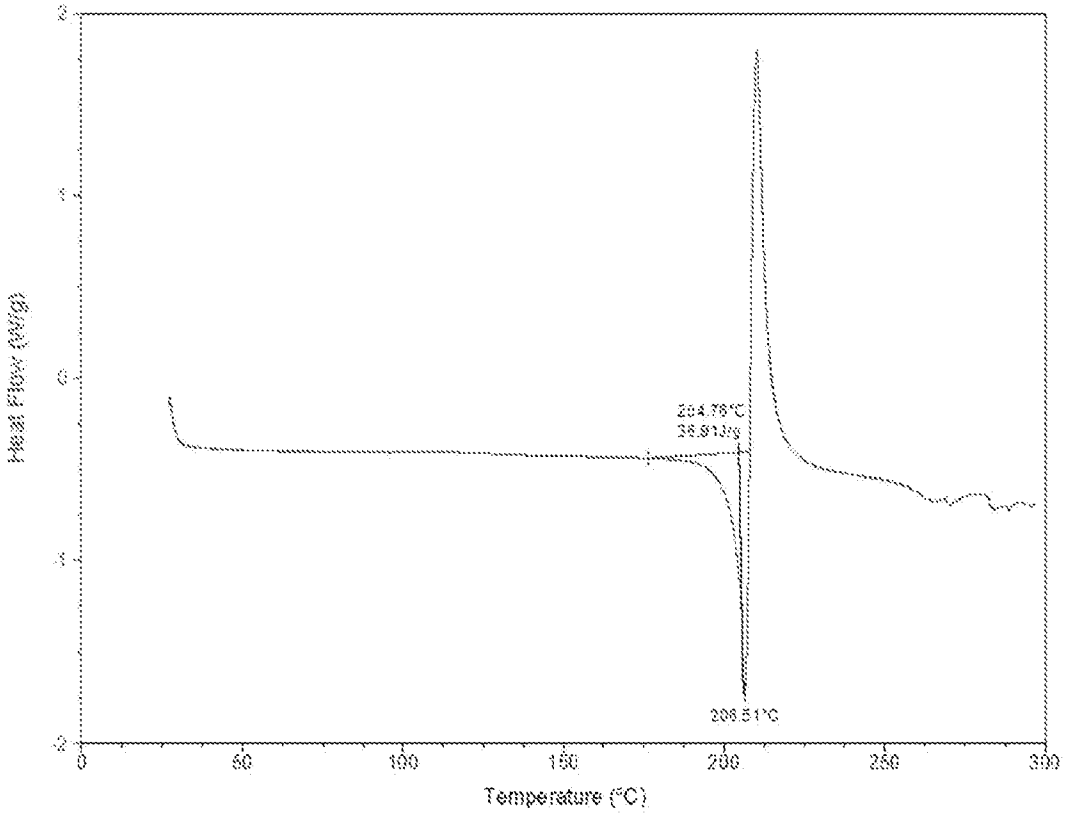

Heat Flow (W/g)
2
1
0
-1
-2
204.76°C
206.51°C
0
50
100
150
200
250
300
Temperature (°C)

FIG. 4

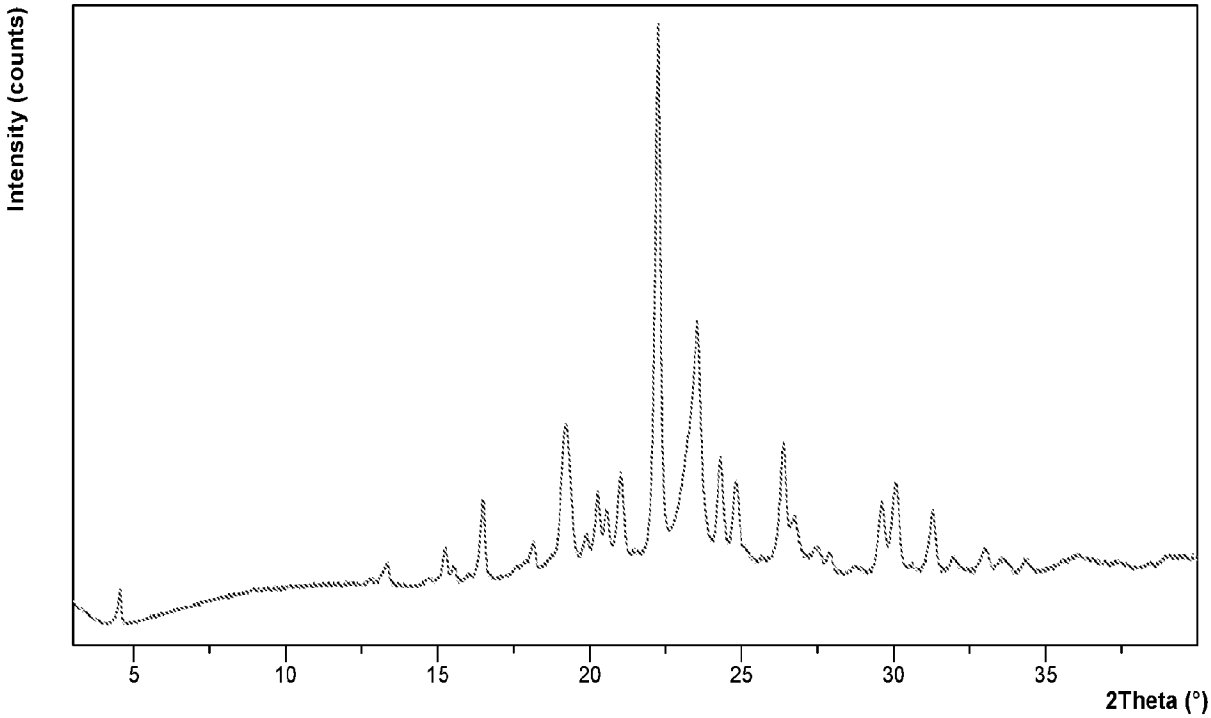


FIG. 5

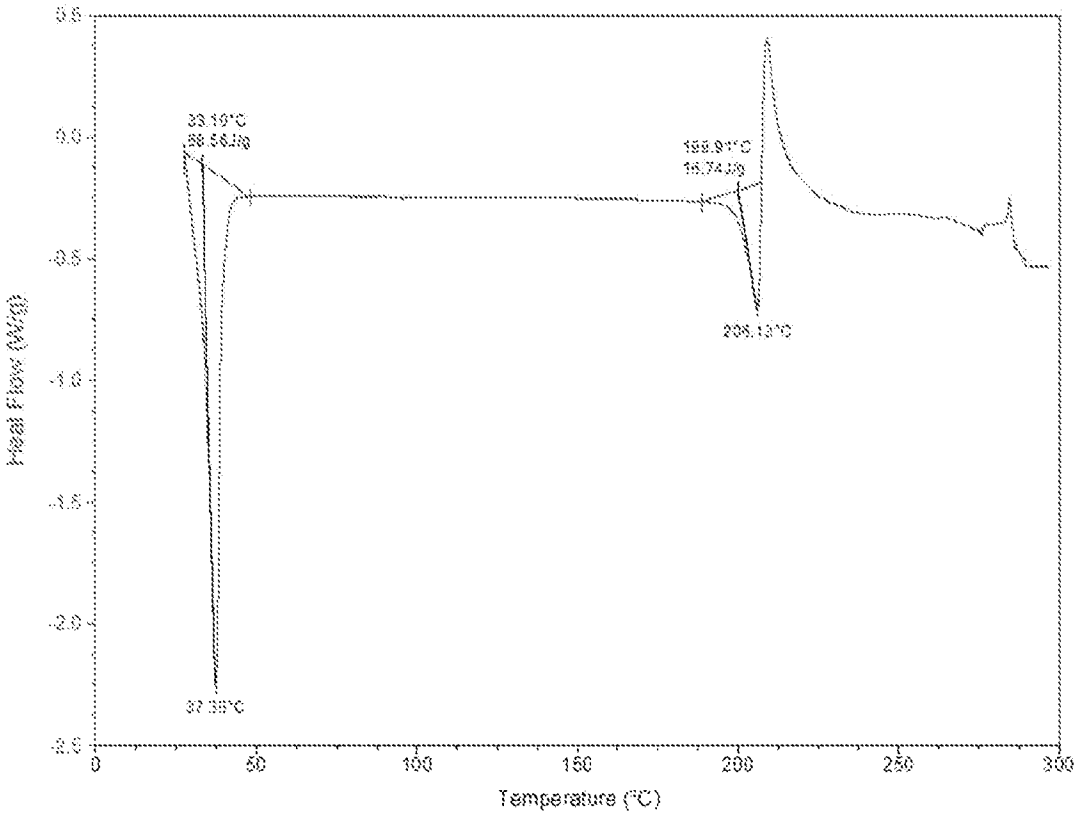

0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
0
50
100
150
200
250
300
Temperature (°C)
33.19°C
88.56J/g
156.91°C
16.74J/g
206.13°C
87.35°C

FIG. 6

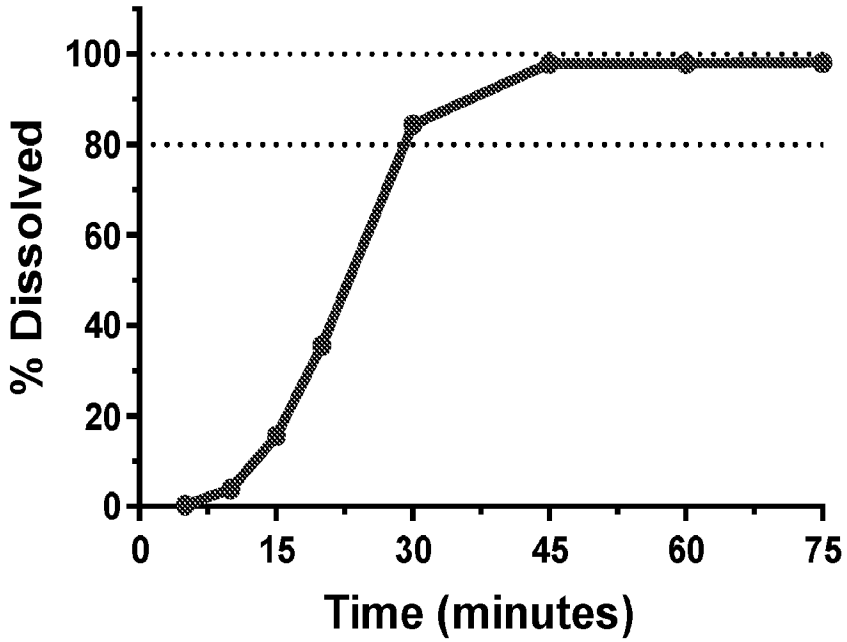
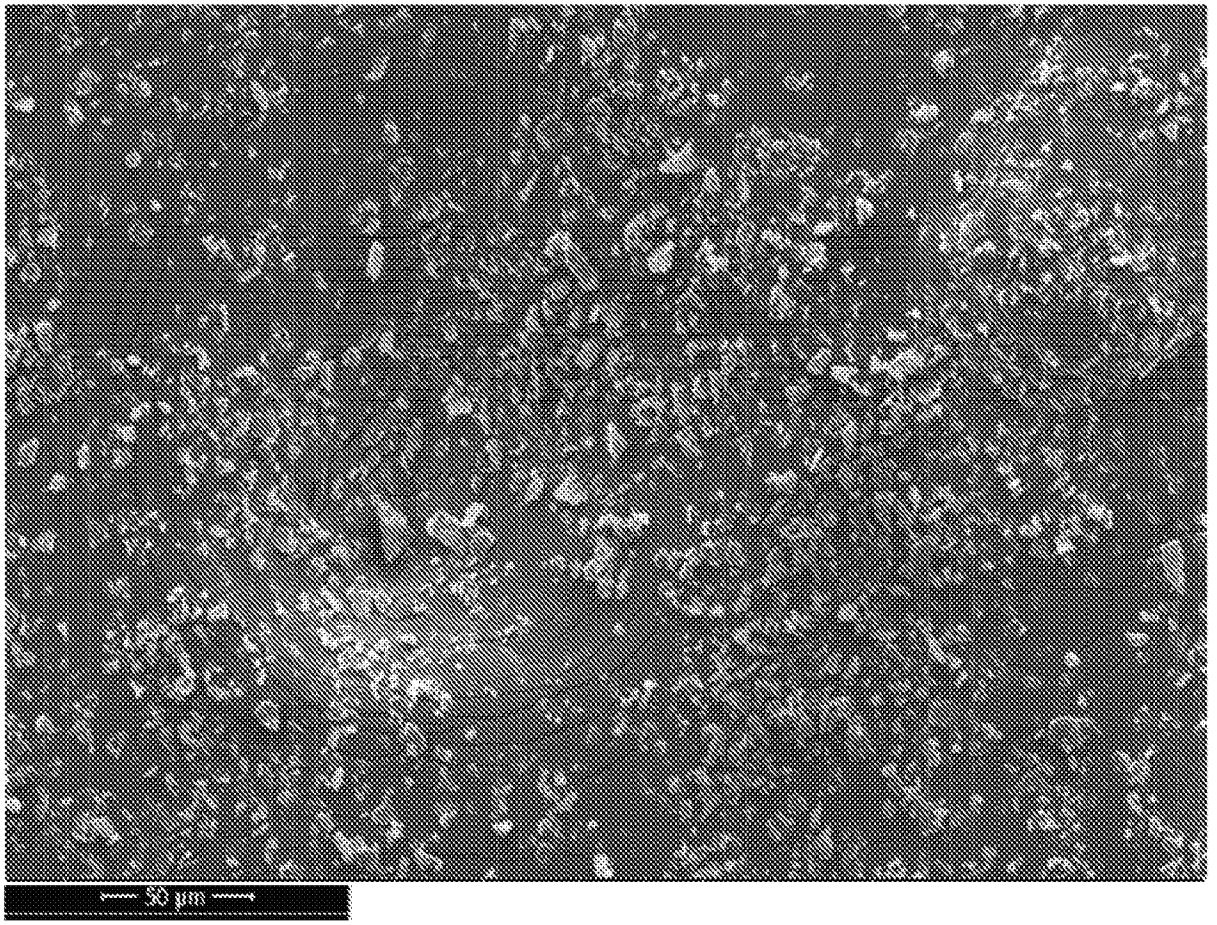


FIG. 7



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/020159

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48 A61K31/435 A61P29/00
ADD.

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)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/166589 A1 (ANDERSON COREY [US] ET AL) 18 June 2015 (2015-06-18) cited in the application	1-3, 15-17
A	paragraph [0011] - paragraph [0012] paragraph [0302] - paragraph [0303] example 20 table 7	4-14, 18-95

A	US 2011/086899 A1 (WINTERS CONRAD STEWART [CA] ET AL) 14 April 2011 (2011-04-14) claims 1-21 paragraph [0151] - paragraph [0153]	1-95

☐ 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	Date of mailing of the international search report
18 May 2020	28/05/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sindel, Ulrike

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/020159

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015166589 A1	18-06-2015	AU 2014362255 A1	09-06-2016
		AU 2019271928 A1	19-12-2019
		CA 2931550 A1	18-06-2015
		CL 2016001400 A1	16-12-2016
		CN 105814067 A	27-07-2016
		CN 108395452 A	14-08-2018
		CY 1121030 T1	11-12-2019
		DK 3080134 T3	22-10-2018
		EP 3080134 A1	19-10-2016
		EP 3459958 A1	27-03-2019
		ES 2688590 T3	05-11-2018
		GE P20207082 B	10-04-2020
		HR P20181563 T1	30-11-2018
		JP 6463580 B2	06-02-2019
		JP 2017504591 A	09-02-2017
		JP 2019055974 A	11-04-2019
		KR 20160098380 A	18-08-2016
		LT 3080134 T	12-11-2018
		PE 20161131 A1	29-10-2016
		PH 12016501028 A1	04-07-2016
		PL 3080134 T3	31-01-2019
		PT 3080134 T	08-11-2018
		RU 2019117783 A	20-02-2020
		SG 11201604477S A	28-07-2016
		SI 3080134 T1	30-11-2018
		TW 201609779 A	16-03-2016
		TW 201920221 A	01-06-2019
		US 2015166589 A1	18-06-2015
		US 2016009743 A1	14-01-2016
		US 2016376295 A1	29-12-2016
		US 2018044361 A1	15-02-2018
		US 2019276483 A1	12-09-2019
		WO 2015089361 A1	18-06-2015
US 2011086899 A1	14-04-2011	US 2011086899 A1	14-04-2011
		WO 2011047173 A2	21-04-2011