

**TREATMENT OF CHRONIC PAIN OR GASTROINTESTINAL DISORDERS USING
BUPRENORPHINE DIMER**

CROSS-REFERENCES TO RELATED APPLICATIONS

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[0001] This application claims priority to U.S. Provisional Application No. 63/568,538, filed March 22, 2024; and U.S. Provisional Application No. 63/512,783, filed July 10, 2023, each of which is incorporated by reference herein in its entirety for all purposes.

**STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER
FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT**

10

[0002] NOT APPLICABLE

**REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER
PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK**

[0003] NOT APPLICABLE

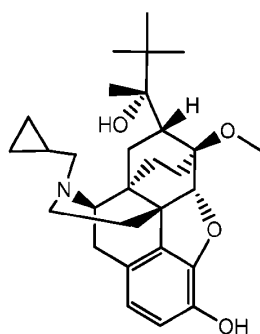
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BACKGROUND

Buprenorphine

[0004] Buprenorphine is a semi-synthetic, mixed μ agonist– κ -antagonist opioid receptor modulator that is used to treat opioid addiction in higher dosages, to control moderate acute pain in non-opioid-tolerant individuals in lower dosages and to control moderate chronic pain in even smaller doses. Its structure is:

20



Buprenorphine

[0005] Buprenorphine is currently indicated for the treatment of pain as intravenous, sublingual and transdermal dosage forms. Buprenorphine is also indicated for the treatment of opiate addiction. However, the oral bioavailability of buprenorphine is very low due to extensive presystemic extraction. Consequently sublingual administration of buprenorphine is required to
5 achieve clinically effective systemic plasma concentrations. Even with sublingual administration, buprenorphine is only about 30% available to systemic circulation.

Chronic Pain

[0006] Chronic pain may be divided into two major categories: “nociceptive” pain (caused by inflamed or damaged tissue that activates specialized pain sensors called nociceptors), and
10 “neuropathic” pain (caused by damage to or malfunction of the nervous system). Neuropathic pain may either be “peripheral”, which originates in the peripheral nervous system, or “central”, which originates in the brain or spinal cord.

[0007] Peripheral neuropathic pain is a chronic condition that is very common in clinical practice. Peripheral neuropathic pain can have many underlying causes, including diabetes,
15 alcoholism, vitamin deficiencies, injury, toxic reactions to prescribed drugs, infectious diseases, malignancies, etc.

[0008] Several mechanisms contribute to the development and severity of neuropathic pain, which are very different from the mechanisms that cause nociceptive pain. As a result of nerve damage, several pathologic changes may occur including: Impulse generation within the
20 damaged nerve fiber; Nerve fiber to nerve fiber interactions; Failure of the normal nerve fiber inhibitory mechanisms; Plasticity—degeneration and regeneration of the injured nerve; and fibers that results in altered conductivity.

[0009] The pain associated with peripheral neuropathy may be severe and, unlike most pain that sufferers have previously experienced, it is characterized by allodynia (pain response from
25 stimuli that do not normally provoke pain), hyperalgesia and in some cases, sensory loss. The pain is often described as “burning, stabbing, raw or sickening”. It can be constant or paroxysmal and with or without sensory impairment. The type and severity of pain or sensory loss depends on the underlying cause of the neuropathy. In chronic forms of neuropathic pain, symptoms begin subtly and progress slowly. Some people may have periods of relief followed

by relapse. Others may reach a plateau stage where symptoms stay the same for many months or years. Many chronic neuropathies worsen over time. For the majority of patients with neuropathic pain, the pain will persist for life. Comorbidities such as depression, poor quality of life and employment and domestic issues are very common.

- 5 **[0010]** More than 100 types of peripheral neuropathy have been identified, each with its own symptoms and prognosis. In general, peripheral neuropathies are classified according to the type of damage to the nerves. Some forms of neuropathy involve damage to only one nerve and are called mononeuropathies. More frequently, however, multiple nerves are affected, called polyneuropathy.
- 10 **[0011]** Many different drugs with a variety of mechanisms of action have been used to treat neuropathic pain, among them the opioids oxycodone and tramadol (Ultram™). None have had complete success and all have significant associated adverse events. A common adverse event of opioid analgesics is sedation, related to the central nervous system effects of these drugs. In many patients, especially elderly patients, treatment with opioid analgesics may result in
- 15 problems of impairment and mobility, which may increase the risk of hip fractures. All patients that use opioid analgesics on a chronic basis will develop physical dependence and stopping the medication for any reason would require them to be under close medical care.
- 20 **[0012]** Buprenorphine, a partial opioid mu (μ) agonist and full opioid delta (δ) and kappa (κ) antagonist, has been extensively studied in patients with neuropathic pain. As an analgesic, it is approximately 30 times more potent than morphine. Buprenorphine has been shown to not only have an analgesic effect but also to have significant anti-hyperalgesic (anti-hypersensitivity) properties. Hyperalgesia is a component of neuropathic pain. The major drawback of prescribing buprenorphine for this purpose is that, as an opioid μ -receptor agonist, it has significant addictive properties and would not be suited for safe long-term use.
- 25 **[0013]** Peripheral neuropathic pain is by nature local, affecting one or more areas of the body and the doses required to treat the local condition by intravenous delivery would seem to rule out buprenorphine itself for this purpose. For the treatment of opioid dependence, it is true that buprenorphine has previously been formulated for subcutaneous long-acting depot injection. (See U.S. Pat. Nos. 8,921,387 and 8,975,270). A buprenorphine depot formulation for the

treatment of peripheral neuropathic pain, however, would appear to offer irreconcilable choices between sufficient dose to treat local pain and other concerns about the agent's access to the central nervous system and its significant consequences.

5 [0014] There has accordingly been a long-felt need for a treatment for peripheral neuropathic pain that offers analgesic properties akin to those of buprenorphine but without the adverse effects expected to accrue from use of the opioid for that purpose.

[0015] A buprenorphine dimer is a homo-dimer including two buprenorphine moieties conjugated to each other by O-alkylation through their phenolic groups, as disclosed in U.S. Patent No. 9,321,780. The dimer has been shown to retain the receptor affinity and
10 pharmacologic characteristics of the parent compound, buprenorphine. It maintains potent binding affinities for the mu (μ), delta (δ), and kappa (κ) receptors. The molecular weight of the dimer is about 961.32 Daltons, which prevents it from being absorbed and entering the central nervous system. As described in U.S. Patent No. 9,549,924, a buprenorphine dimer can be used for treating peripheral neuropathic pain, however requiring parenterally administering the
15 buprenorphine dimer to a patient.

[0016] In view of the foregoing, there remains a need for developing an oral form of an effective non-analgesic drug for treat neuropathic pain, without the adverse effects expected to accrue from use of the opioid (e.g., buprenorphine). The present disclosure meets the need.

Diarrhea-Predominant Irritable Bowel Syndrome

20 [0017] Irritable Bowel Syndrome with Diarrhea (IBS-D) is a highly prevalent gastrointestinal disorder that is often accompanied, in addition to diarrhea, by both visceral and somatic hyperalgesia (enhanced pain from colorectal and somatic stimuli), discomfort, bloating, and gas.

[0018] According to the International Foundation for Functional Gastrointestinal Disorders, IBS-D is estimated to affect between 25-45 million Americans. It is the most common diagnosis
25 made by gastroenterologists, and is one of the disorders most frequently treated by primary care physicians.

[0019] Irritable bowel syndrome has a very heavy impact on the quality of life and has high social costs. The disease has a fluctuating trend, but tends to be chronic or subchronic.

Although there is no evidence that the presence of IBS involves deterioration in patient life expectancy, it significantly reduces health-related quality of life and work productivity. In the more severe cases patients may experience several episodes of abdominal pain and diarrhea per day resulting in severe impairment of relationships and in the workplace.

- 5 [0020] Serum C4 (7 α -hydroxy-4-cholesten-3-one) is an inflammatory marker used to screen IBS-D patients from patients suffering from Inflammatory Bowel Disease IBD and Bile Acid Diarrhea (BAD). Serum C4 levels in general are not elevated in IBS-D patients, and are often below 48 ng/ml in IBS-D patients, as the symptoms are not due to inflammatory damage or bile acid malabsorption. Because the cause of abdominal pain and diarrhea in IBS-D is not
10 known, it is difficult develop or discover mechanism of action-based treatments or pharmaceutical intervention for IBS-D.

IBS-D Treatments

- [0021] Most of the existing treatments control IBS-D by inducing constipation via full mu agonism. Bile acid binders, amitriptyline, probiotics, mast cell stabilizers and 5-ASA have been
15 used off-label in the treatment of IBS-D, albeit without compelling evidence of chronic efficacy. The anti-diarrheal loperamide, a synthetic opioid, has been used similarly, but its uninhibited full μ opioid agonist activity often results in severe constipation.

- [0022] Among drugs in development for IBS-D is LX 1033, an inhibitor of serotonin synthesis in the gastro-intestinal tract, currently being developed by Lexicon Pharmaceuticals. Its
20 mechanism of action, however, does not support pain alleviation. DNK-333 (Novartis), a neurokinin antagonist, was withdrawn from study for IBS-D following Phase II studies for want of efficacy. Ibodutant (Menarini), another neurokinin antagonist in Phase II trials, showed no efficacy over placebo in the overall population, and is being pursued in further testing only in women. Rifaximin (Salix Pharmaceuticals) has been studied for IBS-D, showing moderate
25 activity, but there is significant concern for the development of antibiotic resistance and continued efficacy.

[0023] Latronex (alosetron, Prometheus Laboratories, Inc.) is the only drug approved for IBS-D in the United States, albeit only for women. It has no demonstrated analgesic properties.

Importantly, it has a black box warning for serious adverse effects including, specifically, ischemic colitis.

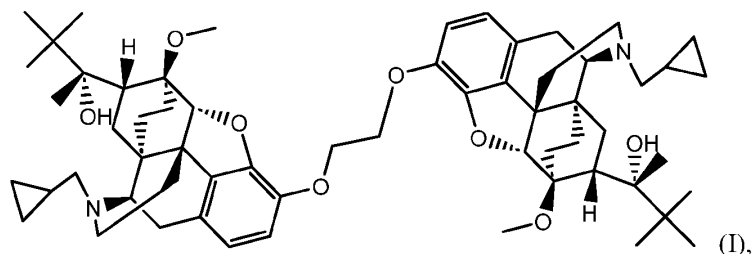
[0024] To date, no drug has been approved in the United States for chronic, unrestricted treatment of IBS-D.

5 [0025] Eluxadoline (Forest Laboratories, Inc.) is a μ opioid receptor agonist and δ opioid receptor antagonist that has met primary endpoints of improvement of stool consistency and reduction of abdominal pain in Phase III testing. Its effect on pain reduction is modest at best and without a demonstrable effect on reducing colonic hypersensitivity that results in hyperalgesia. Moreover, several cases of pancreatitis, a potentially life threatening disease, were
10 reported in Phase II trials. Cases of pancreatitis were reported even after patients with a known history of biliary disease were excluded from clinical study enrollment. In general, μ agonists have a constricting effect on the Sphincter of Oddi, a muscular valve that regulates the flow of bile and pancreatic juice from the bile duct into the duodenum. Buprenorphine, because of its partial μ agonist effect and κ antagonist effect, does not result in increased tone or constriction of
15 the Sphincter of Oddi. We expect that the buprenorphine dimer, with the same receptor pharmacology as buprenorphine, will also have no constricting effect on the Sphincter of Oddi.

[0026] There has accordingly been a long-standing need for a chronic treatment of IBS-D that decreases intestinal motility, thereby decreasing the incidence of diarrhea, is an analgesic, is not associated with pancreatitis, and more than merely treating symptoms, potentially addresses
20 underlying hypersensitivity and resulting hyperalgesia associated with IBS-D.

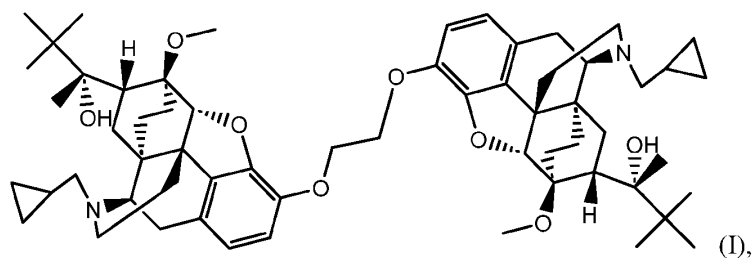
BRIEF SUMMARY OF THE DISCLOSURE

[0027] In one aspect, the present disclosure provides a method of treating a disease in a human subject in need thereof, the method including orally administering to the subject a therapeutically
25 effective amount of a buprenorphine dimer represented by formula (I):



or a pharmaceutically acceptable salt thereof, wherein the therapeutically effective amount of the buprenorphine dimer is a total daily dose of at least about 100 mg per day on a salt-free and anhydrous basis; and the administering achieves a plasma concentration of at least about 700
 5 ng/mL in the subject.

[0028] In another aspect, the present disclosure provides a method of treating a chronic pain in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):

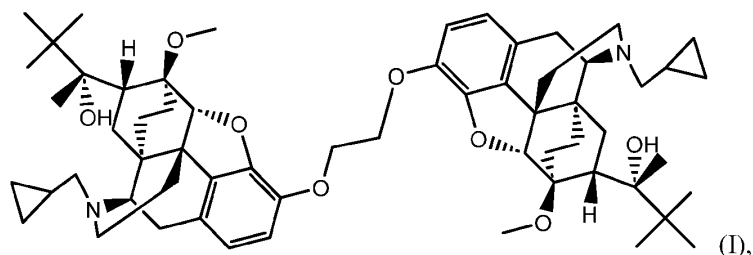


10 or a pharmaceutically acceptable salt thereof, wherein the buprenorphine dimer is administered orally.

[0029] In some embodiments, the buprenorphine dimer is in a neutral form, represented by formula (I).

15 **[0030]** In another aspect, the present disclosure provides a method of treating a chronic pain in a subject in need thereof, the method including administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a buprenorphine dimer in a neutral form represented by formula (I), wherein the pharmaceutical composition is administered orally.

[0031] In another aspect, the present disclosure provides a method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



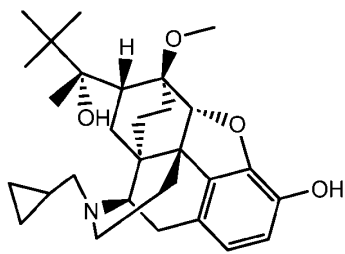
or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a cholecystectomy. In some embodiments, the subject has 7 α -hydroxy-4-cholesten-3-one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

[0032] In some embodiments, the buprenorphine dimer is in a neutral form, represented by formula (I).

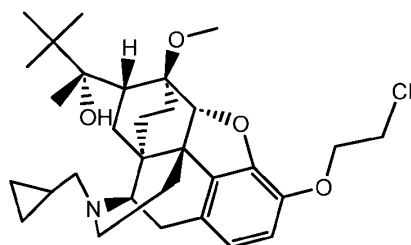
[0033] In another aspect, the present disclosure provides a method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, the method including administering to the subject a pharmaceutical composition including a therapeutically effective amount of a buprenorphine dimer in a neutral form represented by formula (I), wherein the subject has 7 α -hydroxy-4-cholesten-3-one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

[0034] In another aspect, the present disclosure provides a process for preparing a buprenorphine dimer of formula (I) in a neutral form. The process includes:

- a) combining buprenorphine or a salt thereof, represented by the formula:



a first inorganic base, water, and a first phase-transfer agent in 1,2-dichloroethane to form a compound of formula (II):

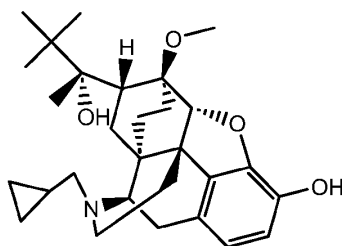


(II); and

- b) combining the compound of formula (II), buprenorphine or a salt thereof, a second
 5 inorganic base, water, and a second phase-transfer agent in an aprotic solvent to provide the buprenorphine dimer of formula (I) in a neutral form.

[0035] In another aspect, the present disclosure provides a process preparing a buprenorphine dimer in a neutral form, represented by formula (I), the process including:

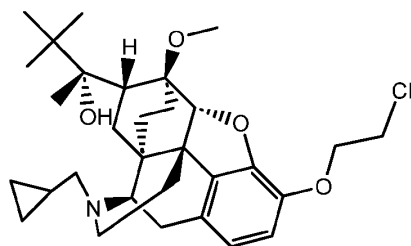
- a) combining a buprenorphine HCl salt, represented by the formula:



HCl

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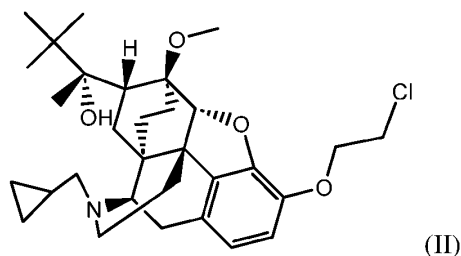
an aqueous NaOH solution, and tetrabutylammonium hydroxide in 1,2-dichloroethane to form a compound of formula (II):



(II); and

- b) combining the compound of formula (II), a buprenorphine HCl salt, an aqueous NaOH
 15 solution, and tetrabutylammonium hydroxide in toluene to provide the buprenorphine dimer of formula (I) in a neutral form.

[0036] In yet another aspect, the present disclosure provides a compound, represented by formula (II) or a salt thereof.



BRIEF DESCRIPTION OF THE DRAWINGS

- 5 [0037] **FIG. 1** shows a study design of spinal nerve ligation induced neuropathic pain in rat (Chung Model), as described in Example 1.
- [0038] **FIG. 2** shows Study 1/Day 14 results of mechanical allodynia in Example 1.
- [0039] **FIG. 3** shows Study 2/Day 22 results of mechanical allodynia in Example 1.
- [0040] **FIG. 4** shows Study 3/Day 38 results of mechanical allodynia in Example 1.
- 10 [0041] **FIGs. 5A-5B** demonstrate an antihyperalgesic response of buprenorphine dimer in normal and sensitized mice after a single dose orally in Example 2. **FIG. 5A**: normal mice; and **FIG. 5B**: sensitized mice.
- [0042] **FIG. 6** demonstrates an antihyperalgesic effect of buprenorphine dimer vs. no antihyperalgesic effect by Eluxadoline, each of which is dosed orally in Example 2.
- 15 [0043] **FIG. 7** demonstrates an antihyperalgesic effect of buprenorphine dimer at low doses in an IBS mouse model in Example 2.
- [0044] **FIGs. 8A-8B** show $C_{\max}$ and AUC_{0-t} of buprenorphine dimer in Phase 1 Clinical Study, Single Ascending Dose (SAD) Study in Example 3. **FIG. 8A**: $C_{\max}$ of buprenorphine dimer; and **FIG. 8B**: AUC_{0-t} of the buprenorphine dimer.
- 20 [0045] **FIGs. 9A-9B** show $C_{\max}$ and AUC_{0-24h} of buprenorphine dimer in Phase 1 Clinical Study, Multiple Ascending Dose (MAD) Study in Example 3. **FIG. 9A**: $C_{\max}$ of buprenorphine

dimer; **FIG. 9B**: AUC_{0-24h} of the buprenorphine dimer; **FIG. 9C**: plasma concentrations of buprenorphine dimer after daily oral dosing for 7 days.

5 [0046] **FIGs. 10A-10B** show spontaneous locomotor activity (LMA) in rats, dosed intravenously with buprenorphine dimer (50 mg/kg), morphine (5 mg/kg), and Eluxadoline (50 mg/kg), respectively, in Example 6. **FIG. 10A**: distance traveling; **FIG. 10B**: time spent traveling; and **FIG. 10C**: vertical rearing.

[0047] **FIG. 11** shows stability of buprenorphine dimer incubated under neutral, acidic, and basic conditions as in Example 7.

10 [0048] **FIG. 12** shows a synthetic scheme for preparing buprenorphine dimer in a neutral form as in Example 8.

[0049] **FIG. 13** shows composite responder proportions by treatment, week 1-12, among patients with normal C4 levels at baseline in Example 10. ITT analysis set excluding COVID-19 per-Protocol affected patients and treating excessive loperamide users as non-responders.

15 [0050] **FIG. 14** shows composite responder proportions by treatment, week 1-12, among post-cholecystectomy patient with normal C4 levels at baseline in Example 10. ITT analysis set excluding COVID-19 per-Protocol affected patients and treating excessive loperamide users as non-responders.

[0051] **FIG. 15** shows therapeutic benefit across multiple endpoints in Protocol-compliant patients with normal C4 levels, treated with buprenorphine dimer in Example 10.

20 [0052] **FIG. 16** shows therapeutic benefit across multiple endpoints in Protocol-compliant post-cholecystectomy patients with normal C4 levels, treated with buprenorphine dimer in Example 10.

[0053] **FIG. 17** shows therapeutic benefit across multiple endpoints in Protocol-compliant patients with all C4 levels, treated with buprenorphine dimer in Example 10.

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DETAILED DESCRIPTION OF THE DISCLOSURE

I. GENERAL

[0054] The present disclosure provides a method of treating chronic pain in a subject in need thereof by orally administering: i) a therapeutically effective amount of a buprenorphine dimer of formula (I) or a pharmaceutically acceptable salt thereof; or ii) a pharmaceutical composition including a therapeutically effective amount of the buprenorphine dimer of formula (I). In

5 particular, the buprenorphine dimer of formula (I) administered is in a neutral form.

[0055] The present disclosure provides a method of treating IBS-D in a subject who has a normal range of 7 α -hydroxy-4-cholesten-3-one (C4) in blood (e.g., C4 level is no more than 50 mg/dL) by administering: i) a therapeutically effective amount of a buprenorphine dimer of formula (I) or a pharmaceutically acceptable salt thereof; or ii) a pharmaceutical composition

10 including a therapeutically effective amount of the buprenorphine dimer of formula (I). In particular, the buprenorphine dimer of formula (I) administered is in a neutral form.

[0056] The therapeutically effective amount of the buprenorphine dimer of formula (I) provides both analgesic and antihyperalgesic effects, while minimizing one or more unwanted symptoms (e.g., sedation, drowsiness, euphoria, withdrawal symptoms, and respiratory

15 depression), associated with an opioid central effect.

[0057] The present disclosure also provides a process for preparing a buprenorphine dimer in a neutral form, represented by formula (I). The process is suitable for manufacturing an Active Pharmaceutical Ingredient (API) on a large scale for drug development.

II. DEFINITIONS

20 [0058] Unless specifically indicated otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this disclosure belongs. In addition, any method or material similar or equivalent to a method or material described herein can be used in the practice of the present disclosures. For purposes of the present disclosure, the following terms are defined.

25 [0059] Unless specifically indicated otherwise, the group “” as used herein in formula (I) refers to methyl.

[0060] Unless specifically indicated otherwise, a neutral form of the buprenorphine dimer is represented by formula (I), wherein both of the nitrogen atoms are not positively charged (e.g.,

protonated or in a quaternary ammonium cation). The neutral form of the buprenorphine dimer also refers to a free-base form.

[0061] “Comprise,” “include,” and “have,” and the derivatives thereof, are used herein interchangeably as comprehensive, open-ended terms. For example, use of “comprising,”

5 “including,” or “having” means that whatever element is comprised, had, or included, is not the only element encompassed by the subject of the clause that contains the verb.

[0062] “Base” refers to a functional group that deprotonates water to produce a hydroxide ion. Bases useful in the present invention include inorganic bases. Exemplary inorganic bases include alkali bicarbonates, alkali carbonates, alkali phosphates tribasic, alkali phosphate dibasic,
10 alkali hydroxides, and alkali hydride, as defined herein.

[0063] “First inorganic base” and “second inorganic base” refer to a base as defined above and described in embodiments of the present invention. The base naming conventions are used solely for the purpose of clarity in relevant steps of the process as described herein and they are not required to be in a numerical order. One skilled in the art will understand the meaning of
15 these base naming conventions (‘first inorganic base’, ‘second inorganic base’) within the context of the term’s use in the embodiments and claims herein.

[0064] “Alkali hydroxide” refers to a class of chemical compounds which are composed of an alkali metal cation and the hydroxide anion (OH^-). Alkali hydroxides useful in the present invention include lithium hydroxide (LiOH), sodium hydroxide (NaOH), potassium hydroxide
20 (KOH), and cesium hydroxide (CsOH).

[0065] “Aprotic solvent” refers to solvents that lack an acidic hydrogen. Consequently, they are not hydrogen bond donors. Common characteristics of aprotic solvents are solvents that can accept hydrogen bonds, solvents do not have acidic hydrogen, and solvents dissolve salts. Examples of aprotic solvents include, but are not limited to, N-methylpyrrolidone (NMP),
25 tetrahydrofuran (THF), 2-methyl tetrahydrofuran (MeTHF), ethyl acetate (EtOAc), acetone, dimethylformamide (DMF), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), propylene carbonate (PC), and hexamethylphosphoramide (HMPA).

[0066] “Phase-transfer agent” or “phase-transfer catalyst (PTC)” refers to a catalyst that facilitates the migration of a reactant from one phase into another phase where reaction occurs.

Phase-transfer catalysis is a special form of heterogeneous catalysis. Ionic reactants are often soluble in an aqueous phase but insoluble in an organic phase in the absence of the phase-transfer catalyst. The catalyst functions like a detergent for solubilizing the salts into the organic phase. By using a PTC process, one can achieve faster reactions, obtain higher conversions or yields, make fewer byproducts, eliminate the need for expensive or dangerous solvents that will dissolve all the reactants in one phase, eliminate the need for expensive raw materials and/or minimize waste problems. PTC is not limited to systems with hydrophilic and hydrophobic reactants. PTC is sometimes employed in liquid/solid and liquid/gas reactions. As the name implies, one or more of the reactants are transported into a second phase which contains both reactants.

10 Phase-transfer catalysts for anionic reactants are often quaternary ammonium salts.

[0067] “First phase-transfer agent” and “second phase-transfer agent” refer to a phase-transfer agent as defined above and described in embodiments of the present invention. The phase-transfer agent naming conventions are used solely for the purpose of clarity in relevant steps of the process as described herein and they are not required to be in a numerical order. One skilled in the art will understand the meaning of these phase-transfer agent naming conventions (‘first phase-transfer agent’, ‘second phase-transfer agent’) within the context of the term’s use in the embodiments and claims herein.

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[0068] “Quaternary ammonium salt” refers to a salt of a quaternary ammonium cation, as defined herein. Quaternary ammonium cation, also known as quat, refers to a positively charged compound having the formula NR_4^+ where R groups can be alkyl, aryl, or a combination thereof. Unlike the ammonium ion (NH_4^+) and the primary, secondary, or tertiary ammonium cations, the quaternary ammonium cations are permanently charged, independent of the pH of their solution.

20

[0069] “About” means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In some embodiments, the term “about” means within a standard deviation using measurements generally acceptable in the art. In some embodiments, “about” means a range extending to $\pm 10\%$ of the specified value. In some embodiments, “about” means $\pm 5\%$ of the specified value.

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[0070] When ranges of values are disclosed, and the notation “from n_1 ... to n_2 ” or “between n_1 ... and n_2 ” is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this

notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range “from 1 mg to 3 mg (milligram),” which is intended to include 1 mg, 3 mg, and everything in between to any number of significant figures (e.g., 1.255 mg, 2.1 mg, 2.9999 mg, etc.).

- 5 [0071] “Salt” refers to acid or base salts of the compounds of the present disclosure. Illustrative examples of pharmaceutically acceptable acid addition salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts and organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable
- 10 pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

- [0072] “Pharmaceutically acceptable excipient” refers to a substance that aids the administration of an active agent to and absorption by a subject. Pharmaceutical excipients useful in the present disclosure include, but are not limited to, binders, fillers, glidants,
- 15 disintegrants, surfactants, lubricants, coatings, sweeteners, flavors, and colors. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present disclosure.

- [0073] “Tablet” refers to solid pharmaceutical formulations with and without a coating. The term “tablet” also refers to tablets having one, two, three or even more layers, wherein each of the before mentioned types of tablets may be without or with one or more coatings. In some
- 20 embodiments, tablets of the present disclosure can be prepared by roller compaction or other suitable means known in the art. The term “tablet” also comprises mini, melt, chewable, effervescent, and orally disintegrating tablets. Tablets include the buprenorphine dimer of formula (I) and one or more pharmaceutical excipients selected from one or more fillers, one or more binders, one or more glidants, one or more disintegrants, one or more surfactants, one or
- 25 more binders, and one or more lubricants. Optionally, a coating agent can be also included. For the purposes of calculating percent weight of the tablet formulation, the amount of coating agent is not included in the calculation. That is, the percent weights reported herein are of the uncoated tablet.

[0074] “Administering” refers to therapeutic provision of the compound or a form thereof to a subject, such as by oral administration.

[0075] “Patient” or “subject” refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided
5 herein. Non-limiting examples include humans, non-human primates (e.g., monkeys), goats, pigs, sheep, cows, deer, horses, bovines, rats, mice, rabbits, hamsters, guinea pigs, cats, dogs, and other non-mammalian animals. In some embodiments, the subject is human. In some embodiments, a subject is an adult (e.g., at least 18 years of age). In some embodiments, the subject is less than 18 years of age.

10 [0076] “Therapeutically effective amount” refers to an amount of a compound or of a pharmaceutical composition useful for treating or ameliorating an identified disease or condition, or for exhibiting a detectable therapeutic or inhibitory effect. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by clinicians, pharmacists, and the like
15 (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

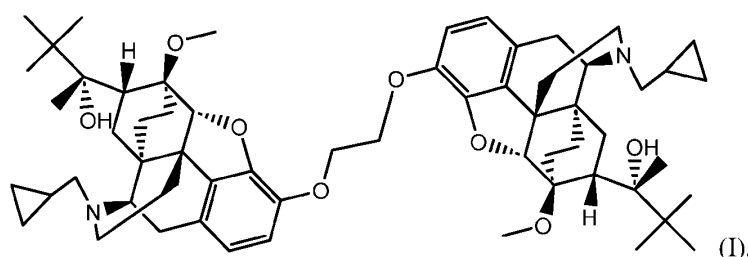
[0077] “Treat”, “treating,” and “treatment” refer to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective
20 parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, assay (e.g., analysis of a
25 fluid of a subject, such as blood, plasma, or urine), imaging analysis, neuropsychiatric exams, and/or a psychiatric evaluation.

[0078] Unless specifically indicated otherwise, the content of the buprenorphine dimer of formula (I) in, e.g., a tablet formulation is calculated based on the normalized weight of the

buprenorphine dimer of formula (I) on a salt-free and anhydrous basis. That is, the salt and/or water content in the buprenorphine dimer of formula (I) is not included in the calculation.

III. METHOD

[0079] In one aspect, the present disclosure provides a method of treating a disease in a human subject in need thereof, the method including orally administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



or a pharmaceutically acceptable salt thereof, wherein the therapeutically effective amount of the buprenorphine dimer is a total daily dose of at least about 100 mg per day on a salt-free and anhydrous basis; and the administering achieves a plasma concentration of at least about 700 ng/mL in the subject. In some embodiments, the administering achieves a plasma concentration of between about 700 ng/mL and about 2400 ng/mL in the subject. In some embodiments, the administering achieves a plasma concentration of between about 700 ng/mL and about 1600 ng/mL in the subject. In some embodiments, the plasma concentration of at least about 700 ng/mL in the subject is a steady state plasma concentration.

[0080] In some embodiments, the buprenorphine dimer is in a neutral form, represented by formula (I).

[0081] In some embodiments, the therapeutically effective amount of the buprenorphine dimer is a total daily dose of at least about 100 mg per day on a salt-free and anhydrous basis, e.g. 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, or 500 mg per day, or any amount therebetween. In some embodiments, the therapeutically effective amount of the buprenorphine dimer is a total daily dose of at least about 200 mg per day on a salt-free and anhydrous basis.

[0082] In some embodiments, the buprenorphine dimer is administered once daily. For instance, in some embodiments, the therapeutically effective amount of the buprenorphine dimer is a total daily dose of about 100 mg per day on a salt-free and anhydrous basis, administered once daily.

5 [0083] In some embodiments, the buprenorphine dimer is administered twice daily. For instance, in some embodiments, the therapeutically effective amount of the buprenorphine dimer is a total daily dose of about 100 mg per day on a salt-free and anhydrous basis, administered as 50 mg twice daily. For instance, in some embodiments, the therapeutically effective amount of the buprenorphine dimer is a total daily dose of about 200 mg per day on a salt-free and
10 anhydrous basis, administered as 100 mg twice daily.

[0084] In some embodiments, the disease is chronic pain. In some embodiments, the chronic pain is a nociceptive pain, a neuropathic pain, or a combination thereof. In some embodiments, the chronic pain is a peripheral chronic pain. In some embodiments, the chronic pain is peripheral neuropathic pain.

15 [0085] In some embodiments, the subject has a sickle cell disease (SCD), cancer and/or under chemotherapy, HIV, diabetes, shingles, a traumatic injury, a surgery, an amputation, a burn, or a combination thereof; and/or the subject has or had a coronavirus disease.

[0086] In some embodiments, the chronic pain is any one of 1) to 10):

- 1) associated with a sickle cell disease (SCD) in the subject;
- 20 2) a chemotherapeutic induced neuropathic pain in the subject who has cancer and under chemotherapy;
- 3) HIV sensory neuropathy;
- 4) a diabetic neuropathy pain;
- 5) a post-herpetic neuralgia in the subject who has or had shingles;
- 25 6) a post-trauma chronic pain;
- 7) a post-surgical pain;
- 8) a post-amputation pain;
- 9) a post-burn pain; and
- 10) associated with a long-term effect in the subject who had a coronavirus disease.

[0087] In some embodiments, the therapeutically effective amount of the buprenorphine dimer reduces the chronic pain, measured by one or more criteria selected from the group consisting of:

- 1) a reduced monthly average score on a 0-10 Likert scale over past 1, 3, or 6 months, relative to a monthly average score prior to the treating;
- 5 2) a reduced monthly average score of characteristic pain intensity and/or disability over past 1, 3, or 6 months, relative to a monthly average score prior to the treating; and
- 3) a reduced pain severity over past 1, 3, or 6 months relative to a pain severity prior to the treating, wherein the reduced pain severity is selected from the group consisting of:
 - 10 i) from Grade 4 (high disability-severely limiting) to any one of Grade 3 (high disability-moderately limiting), Grade 2 (low disability-high intensity), Grade 1 (low disability-low intensity), and Grade 0 (no pain);
 - ii) from Grade 3 to any one of Grade 2, Grade 1, and Grade 0;
 - iii) from Grade 2 to Grade 1 or Grade 0; and
 - iv) from Grade 1 to Grade 0

- 15 **[0088]** In some embodiments, the therapeutically effective amount of the buprenorphine dimer provides an antihyperalgesic effect. In some embodiments, during or after the treating, the subject has reduced hyperalgesia or is substantially free of hyperalgesia. In some embodiments, during or after the treating, the subject is free of hyperalgesia.

- 20 **[0089]** In some embodiments, the disease is Irritable Bowel Syndrome with Diarrhea (IBS-D). In some embodiments, prior to the treating, the subject has worst abdominal pain over past 24 hours in a weekly average score of more than 3, based on a 1-10 numeric rating scale. In some embodiments, prior to the treating, the subject has stool consistency in a weekly average score of greater than 5, as assessed via Bristol Stool Form Score (BSFS).

[0090] In some embodiments, the subject has cholecystectomy.

- 25 **[0091]** In some embodiments, during the treating, the subject receives loperamide. In some embodiments, during the treating, the subject receives loperamide in a total dosage of no more than any one of 8 mg over 24 hours, 14 mg over 48 hours, and 22 mg over 7 days.

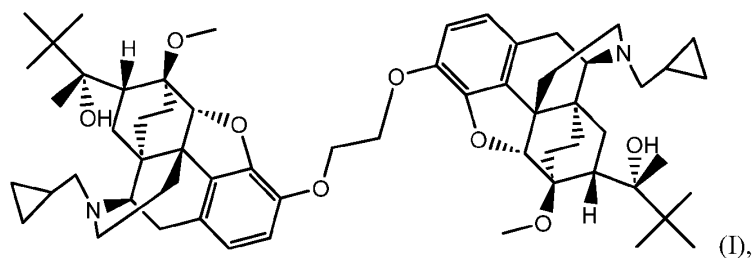
[0092] In some embodiments, during the treating, the subject does not receive loperamide.

[0093] In some embodiments, the therapeutically effective amount of the buprenorphine dimer reduces one or more symptoms associated with IBS-D. In some embodiments, the therapeutically effective amount of the buprenorphine dimer

- 1) reduces a weekly average score of worst abdominal pain over past 24 hours by at least 30%, relative to the weekly average score prior to the treating; and/or
- 2) improves stool consistency, measured by i) a reduced average BSFS score to less than 6, or ii) an absence of a bowel movement provided that features of 1) are met

[0094] In some embodiments, the subject has a C4 level of from about 15 mg/dL to about 45 mg/dL in blood.

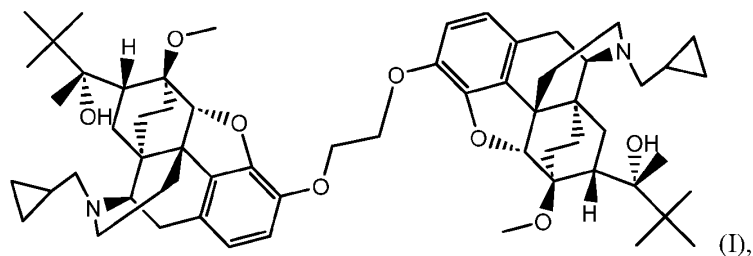
- 10 [0095] In another aspect, the present disclosure provides a method of treating a chronic pain in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



- 15 or a pharmaceutically acceptable salt thereof, wherein the buprenorphine dimer is administered orally.

[0096] In another aspect, the present disclosure provides a method of treating a chronic pain in a subject in need thereof, the method including administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a buprenorphine dimer in a neutral form represented by formula (I), wherein the pharmaceutical composition is administered orally.

- 20 [0097] In another, the present disclosure provides a method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



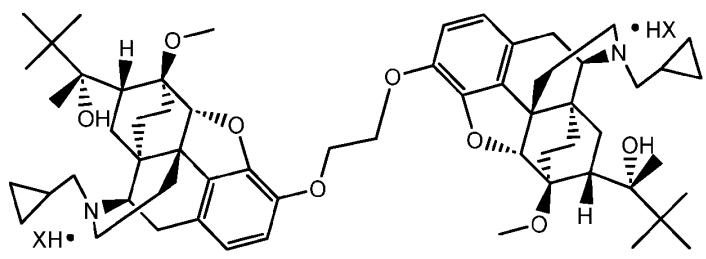
or a pharmaceutically acceptable salt thereof, wherein the subject has 7 α -hydroxy-4-cholesten-3-one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

[0098] In another aspect, the present disclosure provides a method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, the method including administering to the subject a pharmaceutical composition including a therapeutically effective amount of a buprenorphine dimer in a neutral form represented by formula (I), wherein the subject has 7 α -hydroxy-4-cholesten-3-one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

10 III-1: Buprenorphine Dimer of Formula (I)

[0099] The buprenorphine dimer of formula (I) can be in a pharmaceutically acceptable salt form or in a neutral form.

[0100] In some embodiments, the buprenorphine dimer of formula (I) is in a mono-salt form, wherein one of the nitrogen atoms forms a pharmaceutically acceptable salt. In some
15 embodiments, the buprenorphine dimer of formula (I) is in a bis-salt form, wherein both of the nitrogen atoms form pharmaceutically acceptable salts. In some embodiments, the buprenorphine dimer of formula (I) is in a bis-salt form represented by formula (Ia):



wherein HX is a pharmaceutically acceptable acid addition.

[0101] Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. In some embodiments, the dimer of formula (I) is in a bis-HCl salt form.

[0102] In some embodiments, the buprenorphine dimer of formula (I) is in a neutral form (e.g., both of the nitrogen atoms in formula (I) are not protonated or in a quaternary ammonium cation).

[0103] In some embodiments, the buprenorphine dimer has the name of (2S,2'S)-2,2'-((4R,4aS,4'R,4a'S,6R,6'R,7R,7aR,7'R,7a'R,12bS,12b'S)-(ethane-1,2-diylbis(oxy))bis(3-(cyclopropylmethyl)-7-methoxy-1,2,3,4,5,6,7,7a-octahydro-4a,7-ethano-4,12-methanobenzofuro[3,2-e]isoquinoline-9,6-diyl))bis(3,3-dimethylbutan-2-ol).

15 III-2: Chronic Pain

[0104] Chronic pain can be a nociceptive pain (caused by inflamed or damaged tissue that activates specialized pain sensors called nociceptors), a neuropathic pain (caused by damage to or malfunction of the nervous system), or a combination of nociceptive and neuropathic pain. In some embodiments, the chronic pain is a nociceptive pain, a neuropathic pain, or a combination thereof. In some embodiments, the chronic pain is a nociceptive pain. In some embodiments, the chronic pain is a neuropathic pain. In some embodiments, the chronic pain is a combination of nociceptive and neuropathic pain.

[0105] Chronic pain or neuropathic pain can be “peripheral”, which originates in the peripheral nervous system. In some embodiments, the chronic pain is a peripheral chronic pain. In some embodiments, the chronic pain is peripheral neuropathic pain (PNP).

[0106] Common types of peripheral neuropathic pain, which can be treated with the buprenorphine dimer of formula (I) or a pharmaceutical composition thereof, include:

- Acute and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP);
- Alcoholic polyneuropathy;

- Chemotherapy-induced polyneuropathy or chemotherapy-induced peripheral neuropathy (CIPN);
- Complex regional pain syndrome (CRPS);
- Entrapment neuropathy (e.g., carpal tunnel syndrome);
- 5 • HIV sensory neuropathy (e.g., distal symmetrical polyneuropathy (DSP));
- Iatrogenic neuralgia (e.g., post-mastectomy pain or post-thoracotomy pain);
- Idiopathic sensory neuropathy;
- Nerve compression or infiltration by tumor;
- Nutritional deficiency-related neuropathies;
- 10 • Painful diabetic neuropathy;
- Phantom limb pain;
- Post-herpetic neuralgia (caused by shingles); and
- Radiation-induced plexopathy.

- [0107] Additional types of chronic pain, which can be treated with the buprenorphine dimer of
- 15 formula (I) or a pharmaceutical composition thereof, include:
- pain, associated with a sickle cell disease (SCD);
 - visceral pain associated with inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) with diarrhea or constipation;
 - abdominal pain in a subject, who is in remission in terms of gastrointestinal (GI)
 - 20 inflammation but continues to experience diarrhea with water stools and abdominal pain;
 - diabetic neuropathy pain;
 - post-trauma chronic pain;
 - post-surgical pain;
 - post-amputation pain (e.g., phantom limb pain);
 - 25 • post-burn pain; and
 - pain, associated with a long-term effect in the subject who had a coronavirus disease.

[0108] In some embodiments, the chronic pain is acute and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), alcoholic polyneuropathy, chemotherapy-induced polyneuropathy or chemotherapy-induced peripheral neuropathy (CIPN), complex

regional pain syndrome, entrapment neuropathy (e.g., carpal tunnel syndrome), HIV sensory neuropathy (e.g., distal symmetrical polyneuropathy (DSP)), iatrogenic neuralgia, idiopathic sensory neuropathy, nerve compression or infiltration by tumor, nutritional deficiency-related neuropathy, diabetic neuropathy, phantom limb pain, post-herpetic neuralgia, radiation-induced plexopathy, or a combination thereof.

[0109] In some embodiments, the chronic pain is acute and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In some embodiments, the chronic pain is alcoholic polyneuropathy. In some embodiments, the chronic pain is chemotherapy-induced polyneuropathy or chemotherapy-induced peripheral neuropathy (CIPN). In some embodiments, the chronic pain is complex regional pain syndrome. In some embodiments, the chronic pain is entrapment neuropathy. In some embodiments, the chronic pain is carpal tunnel syndrome. In some embodiments, the chronic pain is HIV sensory neuropathy. In some embodiments, the chronic pain is distal symmetrical polyneuropathy (DSP). In some embodiments, the chronic pain is iatrogenic neuralgia. In some embodiments, the chronic pain is iatrogenic neuralgia, resulted from a surgical trauma (e.g., post-mastectomy pain or post-thoracotomy pain). In some embodiments, the chronic pain is idiopathic sensory neuropathy. In some embodiments, the chronic pain is associated with nerve compression or infiltration by tumor. In some embodiments, the chronic pain is nutritional deficiency-related neuropathy. In some embodiments, the chronic pain is diabetic neuropathy. In some embodiments, the chronic pain is phantom limb pain. In some embodiments, the chronic pain is post-herpetic neuralgia. In some embodiments, the chronic pain is radiation-induced plexopathy.

[0110] In some embodiments, the chronic pain is associated with a sickle cell disease (SCD) in a subject. In some embodiments, the chronic pain is visceral pain associated with inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) with diarrhea or constipation. In some embodiments, the chronic pain is an abdominal pain in a subject, who is in remission in terms of gastrointestinal (GI) inflammation but continues to experience diarrhea with water stools and abdominal pain. In some embodiments, the chronic pain is diabetic neuropathy pain. In some embodiments, the chronic pain is post-trauma chronic pain. In some embodiments, the chronic pain is post-surgical pain. In some embodiments, the chronic pain is post-amputation pain (e.g., phantom limb pain). In some embodiments, the chronic pain is post-burn pain. In some

embodiments, the chronic pain is associated with a long-term effect in the subject who had a coronavirus disease (e.g., COVID 19).

III-3: Subject

5 [0111] The subject can be a human. In some embodiments, the subject is human. In some embodiments, the human is an adult in an age of at least 18 years old. In some embodiments, the human is less than 18 years of age.

Chronic Pain

10 [0112] The subject has any one of chronic pain as described in Section III-2. In some embodiments, the subject has chronic pain according to any one of embodiments as described in Section III-2.

[0113] In some embodiments, the subject has a sickle cell disease (SCD), cancer or tumor, chemotherapy, radiation, HIV, inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) with diarrhea or constipation, diabetes, shingles, a traumatic injury, a surgery, an amputation, a burn, or a combination thereof; and/or the subject has or had a coronavirus disease.

15 [0114] In some embodiments, the subject has a sickle cell disease (SCD). In some embodiments, the subject has cancer or tumor. In some embodiments, the subject has cancer or tumor under chemotherapy or radiation. In some embodiments, the subject is under chemotherapy for treating cancer or tumor. In some embodiments, the subject is under radiation for treating cancer or tumor. In some embodiments, the subject has HIV. In some embodiments, 20 the subject has IBD or IBS with diarrhea or constipation. In some embodiments, the subject is in remission in terms of gastrointestinal (GI) inflammation but continues to experience diarrhea with water stools and abdominal pain. In some embodiments, the subject has diabetes. In some embodiments, the subject has or had shingles. In some embodiments, the subject has a traumatic injury (e.g., car accidents, gunshot wound, etc.). In some embodiments, the subject has a 25 surgery. In some embodiments, the subject has an amputation. In some embodiments, the subject has a burn (e.g., from car or house fire, or wildfire). In some embodiments, the subject has or had a coronavirus disease (e.g., COVID 19).

Gastrointestinal Disease

[0115] The subject has a diagnosis of IBS-D (Irritable Bowel Syndrome with Diarrhea) and meets the Rome IV Criteria, by history, for both IBS and IBS-D. In some embodiments, the subject has had a cholecystectomy. In some embodiments, the subject has the IBS-D and has a normal level of 7 α -hydroxy-4-cholesten-3-one (C4) in blood or at an slightly elevated level of

5 C4 in blood. In some embodiments, the subject has the IBS-D and a C4 level of no more than 50 mg/dL in blood. In some embodiments, the subject has the IBS-D and a C4 level of from about 15 mg/dL to about 45 mg/dL in blood.

[0116] In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has worst abdominal pain over past 24 hours in a weekly average score of more than 3, based on

10 a 1-10 numeric rating scale.

[0117] In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has stool consistency in a weekly average score of greater than 5, as assessed via Bristol Stool Form Score (BSFS). In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has stool consistency in a weekly average score of greater than 5.5, as assessed via

15 Bristol Stool Form Score (BSFS). In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has stool consistency in a weekly average score of greater than 6, as assessed via Bristol Stool Form Score (BSFS).

[0118] In some embodiments, the subject does not receive loperamide prior to the treatment with the buprenorphine dimer, or discontinues loperamide at least 14 days prior to the treatment

20 with the buprenorphine dimer.

[0119] In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has i) fecal primary bile acids of more than about 4% by weight, and/or ii) fecal bile acids in a total amount of more than about 1,000 μ mol/48h. In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has i) fecal primary bile acids of more than about 4%

25 by weight, and ii) fecal bile acids in a total amount of more than about 1,000 μ mol/48h. In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has fecal bile acids in a total amount of less than about 2,337 μ mol/48h. In some embodiments, prior to the treatment with the buprenorphine dimer, the subject has fecal bile acids in a total amount of from about 1,000 μ mol/48h to about 2,337 μ mol/48h. In some embodiments, prior to the treatment

with the buprenorphine dimer, the subject has i) fecal primary bile acids of more than about 4% by weight, and ii) fecal bile acids in a total amount of from about 1,000 $\mu\text{mol}/48\text{h}$ to about 2,337 $\mu\text{mol}/48\text{h}$.

[0120] In some embodiments, the subject has cholecystectomy.

- 5 [0121] In some embodiments, during the treatment with the buprenorphine dimer, the subject receives loperamide. In some embodiments, during the treatment with the buprenorphine dimer, the subject receives loperamide in a dosage of about 2 mg per every 6 hours. In some
embodiments, during the treatment with the buprenorphine dimer, the subject receives
loperamide in a total dosage of no more than any one of 8 mg over 24 hours, 14 mg over 48
10 hours, and 22 mg over 7 days. In some embodiments, during the treatment with the
buprenorphine dimer, the subject does not receive loperamide.

[0122] In some embodiments, prior to with the buprenorphine dimer, the subject meets all of inclusive criteria:

- 15 • Has a diagnosis of IBS-D (Irritable Bowel Syndrome with Diarrhea) and meets the Rome IV Criteria, by history, for both IBS and IBS-D;
- Completed the daily eDiary for at least 6 of 7 days during the week before the treatment and for at least 11 of 14 days during the two weeks before the treatment;
- Had a weekly average of worst abdominal pain scores in the past 24 hours >3 on a 0 to 10 numeric rating scale for the week prior to the treatment;
- 20 • Had an overall mean weekly stool consistency > 5 as assessed via Bristol Stool Form Score (BSFS) for the week prior to the treatment;
- Had not used loperamide within the 14 days prior to the treatment; and
- Is on a stable diet for the past 12 weeks and is not planning to change lifestyle and/or diet during the treatment.

- 25 [0123] In some embodiments, the subject does not meet any one of exclusion criteria:

- History of clinically relevant pancreatic conditions including pancreatitis, pancreas divisum, or Sphincter of Oddi (SO) dysfunction with pancreatic manifestations;
- History of biliary pathology including acute cholecystitis within 6 months or biliary pain including post-cholecystectomy pain;

- Patients who have had biliary sphincterotomy with post-procedure persistent abnormal liver function transaminases (LFTs);
 - Planned elective surgery within the next 4 months;
 - Significant and/or severe medical illnesses such as cardiovascular, neurological, infectious, renal, hepatic or respiratory disorders that would interfere with the patient's medical care, participation in, or conduct of the study;
 - History of intestinal obstruction, stricture, toxic megacolon, GI (gastro-intestinal) perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation (e.g. aorto-iliac disease);
 - History of lactose intolerance uncontrolled on a lactose-free diet, or other malabsorption syndromes (e.g. fructose malabsorption);
 - Dysphagia or difficulty swallowing pills;
 - History of inflammatory bowel disease, celiac disease, Clostridium difficile colitis or have had recent unexplained GI bleeding within 3 months prior to screening;
 - History of major gastric, hepatic, pancreatic or intestinal surgery (appendectomy, hemorrhoidectomy, or polypectomy allowed as long as occurred > 3 months prior to trial screening; uncomplicated laparoscopic or open cholecystectomy is allowed if no history of post-operative biliary tract pain and surgery occurred > 3 months prior to screening); and
 - Patients >40 years of age at high risk for colon cancer must have had a screening colonoscopy within the past 3 years prior to trial screening visit or > 50 years of age, must have had a normal screening colonoscopy within the past 10 years prior to trial screening visit. Patients with Lynch Syndrome or Familial Polyposis are excluded from the study.
- [0124]** Further inclusion and exclusion criteria for subjects who may benefit from treatment with a buprenorphine dimer of formula (I), such as subjects enrolled in A Double Blind, Placebo Controlled, Phase 2, Responsive Adaptive Randomization Study of the buprenorphine dimer in Patients with Irritable Bowel Syndrome with Diarrhea (IBS D), are described in Example 9.
- [0125]** In some embodiments, the subject meets all of inclusion criteria of 1) to 4) as described in Example 9. In some embodiments, the subject meets all of inclusion criteria of 1) to 4) as

described in Example 9, provided that the subject does not meet any one of exclusion criteria of 1) to 11) as described in Example 9.

III-4: Therapeutically Effective Amount/Administration

5 [0126] The therapeutically effective amount can be a total daily dosage of no more than about 2000 mg of the dimer of formula (I) on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of no more than about 2000 mg, about 1600 mg, about 1200 mg, or about 800 mg of the dimer of formula (I) on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of no more than about 800 mg of the dimer of formula (I) on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of no more than about 400 mg of the dimer of formula (I) on a salt-free and anhydrous basis.

15 [0127] In some embodiments, the therapeutically effective amount is a total daily dosage of from about 50 mg to about 800 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 50 mg to about 400 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 50 mg to about 250 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of from about 50 mg to about 150 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

20 [0128] In some embodiments, the therapeutically effective amount is a total daily dosage of about 100 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 150 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 200 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 250 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 300 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 350 mg of the

buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 400 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 450 mg of the buprenorphine dimer on a salt-free and anhydrous basis. In some embodiments, the therapeutically effective amount is a total daily dosage of about 500 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

[0129] In general, the dimer of formula (I) can be administered orally. In some embodiments, the dimer of formula (I) is administered orally. In some embodiments, the dimer of formula (I) in a neutral form is administered orally. In some embodiments, the dimer of formula (I) in a tablet formulation is administered orally. In some embodiments, the dimer of formula (I) in a neutral form in a tablet formulation is administered orally.

[0130] In general, the dimer of formula (I) can be administered once or multiple times (e.g., 2, 3, 4, or more times) daily. In some embodiments, the dimer of formula (I) is administered once, twice, three times, or four times daily. In some embodiments, the dimer of formula (I) is administered once daily. In some embodiments, the dimer of formula (I) is administered twice daily.

[0131] In some embodiments, the dimer of formula (I) in a neutral form is administered once, twice, three times, or four times daily. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily. In some embodiments, the dimer of formula (I) in a neutral form is administered twice daily.

[0132] In some embodiments, the dimer of formula (I) is administered at least about 30 minutes prior to breakfast. In some embodiments, the dimer of formula (I) is administered once daily at least about 30 minutes prior to breakfast.

[0133] In some embodiments, the dimer of formula (I) in a neutral form is administered at least about 30 minutes prior to breakfast. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily at least about 30 minutes prior to breakfast.

[0134] The dimer of formula (I) can be in an oral dosage form in one or more dosage strengths, where the dimer of formula (I) is present in an amount of from about 5 mg to about 800 mg, on a salt-free and anhydrous basis. In some embodiments, the oral dosage form is a tablet

formulation in one or more dosage strengths. In some embodiments of the tablet formulation, the dimer of formula (I) is present in an amount of about 5 mg, 10 mg, 15 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, or 500 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) is present in an amount of about 25 mg, 50 mg, or 100 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) is present in an amount of about 25 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) is present in an amount of about 50 mg in each tablet, on a salt-free and anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) is present in an amount of about 100 mg in each tablet, on a salt-free and anhydrous basis.

[0135] The dimer of formula (I) in a neutral form can be in an oral dosage form in one or more dosage strengths, where the dimer of formula (I) in a neutral form is present in an amount of from about 5 mg to about 800 mg, on an anhydrous basis. In some embodiments, the oral dosage form is a tablet formulation in one or more dosage strengths. In some embodiments of the tablet formulation, the dimer of formula (I) in a neutral form is present in an amount of about 5 mg, 10 mg, 15 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, or 500 mg in each tablet, on an anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) in a neutral form is present in an amount of about 25 mg, 50 mg, or 100 mg in each tablet, on an anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) in a neutral form is present in an amount of about 25 mg in each tablet, on an anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) in a neutral form is present in an amount of about 50 mg in each tablet, on an anhydrous basis. In some embodiments of the tablet formulation, the dimer of formula (I) in a neutral form is present in an amount of about 100 mg in each tablet, on an anhydrous basis.

[0136] The tablet including the buprenorphine dimer of formula (I) can be an immediate-release tablet or a time-release tablet. In some embodiments, the tablet including the buprenorphine dimer of formula (I) is an immediate-release tablet.

[0137] The tablet including the buprenorphine dimer of formula (I) in a neutral form can be an immediate-release tablet or a time-release tablet. In some embodiments, the tablet including the buprenorphine dimer of formula (I) in a neutral form is an immediate-release tablet.

5 [0138] In some embodiments, the dimer of formula (I) is administered once daily to provide a total daily dosage of no more than about 2000 mg, about 1600 mg, about 1200 mg, or about 800 mg of the dimer, on a salt-free and anhydrous basis. In some embodiments, the dimer of formula (I) is administered once daily to provide a total daily dosage of no more than about 800 mg of the dimer, on a salt-free and anhydrous basis. In some embodiments, the dimer of formula (I) is administered once daily to provide a total daily dosage of no more than about 400 mg of the
10 dimer, on a salt-free and anhydrous basis.

[0139] In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of no more than about 2000 mg, about 1600 mg, about 1200 mg, or about 800 mg of the dimer, on an anhydrous basis. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of no
15 more than about 800 mg of the dimer, on an anhydrous basis. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of no more than about 400 mg of the dimer, on an anhydrous basis.

[0140] In some embodiments, the dimer of formula (I) is administered once daily to provide a total daily dosage of from about 50 mg to about 800 mg of the dimer, on a salt-free and
20 anhydrous basis. In some embodiments, the dimer of formula (I) is administered once daily to provide a total daily dosage of from about 50 mg to about 400 mg of the dimer, on a salt-free and anhydrous basis. In some embodiments, the dimer of formula (I) is administered once daily to provide a total daily dosage of from about 50 mg to about 250 mg of the dimer, on a salt-free and anhydrous basis. In some embodiments, the dimer of formula (I) is administered once daily to
25 provide a total daily dosage of from about 50 mg to about 150 mg of the dimer, on a salt-free and anhydrous basis. In some embodiments, the dimer of formula (I) is administered once daily to provide a total daily dosage of about 100 mg of the dimer, on a salt-free and anhydrous basis.

[0141] In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of from about 50 mg to about 800 mg of the dimer, on an

anhydrous basis. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of from about 50 mg to about 400 mg of the dimer, on an anhydrous basis. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of from about 50 mg to about 250 mg of the dimer, on an anhydrous basis. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of from about 50 mg to about 150 mg of the dimer, on an anhydrous basis. In some embodiments, the dimer of formula (I) in a neutral form is administered once daily to provide a total daily dosage of about 100 mg of the dimer, on an anhydrous basis.

5 [0142] In general, the subject can be treated with the dimer of formula (I) for a period of at least 12 weeks or for a long-term treatment. In some embodiments, the subject is treated with the dimer of formula (I) for a period of at least 12 weeks. In some embodiments, the subject is treated with the dimer of formula (I) for a period of at least 6 months. In some embodiments, the subject is treated with the dimer of formula (I) for a period of at least one year. In some
10 embodiments, the subject is under a long-term treatment with the dimer of formula (I).

[0143] In some embodiments, the subject is treated with the dimer of formula (I) in a neutral form for a period of at least 12 weeks. In some embodiments, the subject is treated with the dimer of formula (I) in a neutral form for a period of at least 6 months. In some embodiments, the subject is treated with the dimer of formula (I) in a neutral form for a period of at least one
15 year. In some embodiments, the subject is under a long-term treatment with the dimer of formula (I) in a neutral form.

III-5: Efficacy

[0144] The therapeutically effective amount of the buprenorphine dimer of formula (I) can reduce any one of chronic pain as described in Section III-2. In some embodiments, the
20 therapeutically effective amount of the buprenorphine dimer of formula (I) reduces chronic pain, as described according to any one of embodiments as described in Section III-2.

[0145] In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) reduces chronic pain, measured by one or more criteria selected from the group consisting of:

- 1) a reduced monthly average score on a 0-10 Likert scale over past 1, 3, or 6 months, relative to a monthly average score prior to the treating;
- 2) a reduced monthly average score of characteristic pain intensity and/or disability over past 1, 3, or 6 months, relative to a monthly average score prior to the treating; and
- 5 3) a reduced pain severity over past 1, 3, or 6 months relative to a pain severity prior to the treating, wherein the reduced pain severity is selected from the group consisting of:
- i) from Grade 4 (high disability-severely limiting) to any one of Grade 3 (high disability-moderately limiting), Grade 2 (low disability-high intensity), Grade 1 (low disability-low intensity), and Grade 0 (no pain);
- 10 ii) from Grade 3 to any one of Grade 2, Grade 1, and Grade 0;
- iii) from Grade 2 to Grade 1 or Grade 0; and
- iv) from Grade 1 to Grade 0.

[0146] In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) reduces chronic pain, measured by 1) a reduced monthly average score on a 0-10 Likert scale over past 1, 3, or 6 months, relative to a monthly average score prior to the treating.

[0147] In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) reduces chronic pain, measured by 2) a reduced monthly average score of characteristic pain intensity and/or disability over past 1, 3, or 6 months, relative to a monthly average score prior to the treating.

20 [0148] In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) reduces chronic pain, measured by 3) a reduced pain severity over past 1, 3, or 6 months relative to a pain severity prior to the treating, wherein the reduced pain severity is selected from the group consisting of:

- i) from Grade 4 (high disability-severely limiting) to any one of Grade 3 (high disability-moderately limiting), Grade 2 (low disability-high intensity), Grade 1 (low disability-low intensity), and Grade 0 (no pain);
- 25 ii) from Grade 3 to any one of Grade 2, Grade 1, and Grade 0;
- iii) from Grade 2 to Grade 1 or Grade 0; and
- iv) from Grade 1 to Grade 0.

[0149] In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) reduces chronic pain, measured by meeting two of criteria 1), 2), and 3) as described herein. In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) reduces chronic pain, measured by meeting all of criteria 1), 2), and 3) as described herein.

[0150] In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) reduces chronic pain for a period of at least 12 weeks without substantially adjusting the total daily dosage. In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) reduces chronic pain for a period of at least 6 months without substantially adjusting the total daily dosage. In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) reduces chronic pain for a period of at least one year without substantially adjusting the total daily dosage. In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) reduces chronic pain for a long-term treatment without substantially adjusting the total daily dosage.

[0151] The therapeutically effective amount of the buprenorphine dimer of formula (I) provides both analgesic and antihyperalgesic effects, while minimizing one or more unwanted symptoms (e.g., sedation, drowsiness, euphoria, withdrawal symptoms, and respiratory depression), associated with an opioid central effect.

[0152] In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) provides an antihyperalgesic effect. In some embodiments, during or after the treating, the subject has reduced hyperalgesia or is substantially free of hyperalgesia. In some embodiments, during or after the treating, hyperalgesia is reduced by at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%. In some embodiments, during or after the treating, the subject is free of hyperalgesia.

[0153] In some embodiments, during or after the treating, the buprenorphine dimer of formula (I) or a metabolite thereof is absent in a central nerve system of the subject. In some embodiments, during or after the treating, the buprenorphine dimer of formula (I) or a metabolite

thereof is absent in a brain of the subject. In some embodiments, during or after the treating, the buprenorphine dimer of formula (I) or a metabolite thereof is absent in a pupil of the subject.

[0154] In some embodiments, during or after the treating, the subject has minimal symptoms selected from the group consisting of sedation, drowsiness, euphoria, withdrawal symptoms, and respiratory depression, each of which is associated with an opioid central effect. In some
5 embodiments, during or after the treating, the subject does not have any one of sedation, drowsiness, euphoria, withdrawal symptoms, and respiratory depression, each of which is associated with an opioid central effect.

[0155] A Double Blind, Placebo Controlled, Phase 2, Responsive Adaptive Randomization
10 Study can evaluate the effects of the buprenorphine dimer in Patients with Irritable Bowel Syndrome with Diarrhea (IBS D), as described in Examples 9 and 10.

[0156] The therapeutically effective amount of the buprenorphine dimer of formula (I) can reduce one or more symptoms associated with IBS-D (e.g., reducing abdominal pain, improving stool consistency, etc.). In some embodiments, the therapeutically effective amount of the
15 buprenorphine dimer of formula (I) reduces one or more symptoms associated with IBS-D. In some embodiments, the therapeutically effective amount of the buprenorphine dimer 1) reduces a weekly average score of worst abdominal pain over past 24 hours by at least 30%, relative to the weekly average score prior to the treatment; and/or 2) improves stool consistency, measured by
20 i) a reduced average BSFS score to less than 6 (e.g., score of 1, 2, 3, 4, or 5), or ii) an absence of a bowel movement provided that features of 1) are met (i.e., a weekly average score of worst abdominal pain over past 24 hours is reduced by at least 30%, relative to the weekly average score prior to the treatment). In some embodiments, the therapeutically effective amount of the buprenorphine dimer 1) reduces a weekly average score of worst abdominal pain over past 24 hours by at least 30%, relative to the weekly average score prior to the treatment; and/or 2)
25 improves stool consistency, measured by i) a reduced average BSFS score to less than 5 (e.g., score of 1, 2, 3, or 4), or ii) an absence of a bowel movement provided that features of 1) are met (i.e., a weekly average score of worst abdominal pain over past 24 hours is reduced by at least 30%, relative to the weekly average score prior to the treatment).

[0157] In some embodiments, the therapeutically effective amount of the buprenorphine dimer of formula (I) meets any one of secondary efficacy endpoints and exploratory endpoints, as described in a Phase 2 study of Example 9.

5 [0158] In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) mitigates one or more symptoms associated with the IBS-D for a period of at least 12 weeks without substantially adjusting the total daily dosage. In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) mitigates one or more symptoms associated with the IBS-D for a period of at least 6 months without substantially adjusting the total daily dosage. In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) mitigates one or more symptoms associated with the IBS-D for a period of at least one year without substantially adjusting the total daily dosage. In some embodiments, administration of a therapeutically effective amount of the dimer of formula (I) mitigates one or more symptoms associated with the IBS-D for a long-term treatment without substantially adjusting the total daily dosage.

15 **III-6: Oral Dosage Form**

[0159] The oral dosage form including the dimer of formula (I) can be in any oral dosage forms including one or more pharmaceutically acceptable carriers and/or excipients. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient.

20 [0160] For preparing oral dosage forms including the dimer of formula (I), pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton PA
25 ("Remington's").

[0161] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

5 [0162] The powders, capsules and tablets preferably contain from 5% or 10% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other excipients, is
10 surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0163] Suitable solid excipients include, but are not limited to, magnesium carbonate; magnesium stearate; talc; pectin; dextrin; starch; tragacanth; a low melting wax; cocoa butter;
15 carbohydrates; sugars including, but not limited to, lactose, sucrose, mannitol, or sorbitol, starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins including, but not limited to, gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl
20 pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0164] Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product
25 identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the dosage forms can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the dimer of formula (I) mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally,
30 stabilizers. In soft capsules, the dimer of formula (I) may be dissolved or suspended in suitable

liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[0165] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the dimer of formula (I) are dispersed
5 homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0166] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions.

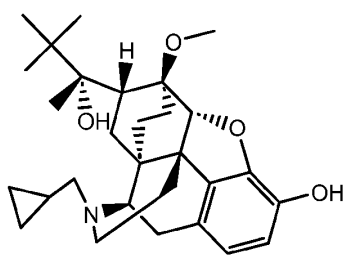
[0167] Aqueous solutions suitable for oral use can be prepared by dissolving the dimer of
10 formula (I) in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents
15 such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a
20 partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

25 [0168] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

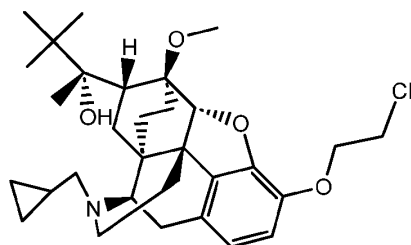
- [0169] Oil suspensions can be formulated by suspending the dimer of formula (I) in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations including the dimer of formula (I) can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these.
- Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

IV. PROCESS FOR PREPARING BUPRENORPHINE DIMER

- [0170] In a third aspect, the present disclosure provides a process for preparing a buprenorphine dimer of formula (I) in a neutral form. The process includes:
- a) combining buprenorphine or a salt thereof, represented by the formula:



a first inorganic base, water, and a first phase-transfer agent in 1,2-dichloroethane to form a compound of formula (II):



(II); and

b) combining the compound of formula (II), buprenorphine or a salt thereof, a second inorganic base, water, and a second phase-transfer agent in an aprotic solvent to provide the buprenorphine dimer of formula (I) in a neutral form.

5 [0171] In some embodiments, the buprenorphine in steps a) and b) are each a buprenorphine HCl salt.

[0172] In some embodiments, the first and second inorganic bases are each an alkali hydroxide. In some embodiments, the first and second inorganic bases are each independently selected from the group consisting of LiOH, NaOH, KOH, and CsOH. In some embodiments, 10 the first and second inorganic bases are each NaOH. In some embodiments, the first and second inorganic bases together with the water are each an aqueous NaOH solution. In some embodiments, the aqueous NaOH solution is a 25% NaOH aqueous solution.

[0173] In some embodiments, the first and/or second phase-transfer agents are independently a quaternary ammonium salt. In some embodiments, the first and second phase-transfer agents are 15 each independently a quaternary ammonium salt. In some embodiments, the first and second phase-transfer agents are each independently a tetrabutylammonium salt. In some embodiments, the first and/or second phase-transfer agents are independently tetrabutylammonium hydroxide or tetrabutylammonium iodide. In some embodiments, the first and second phase-transfer agents are each tetrabutylammonium hydroxide (TBAOH).

20 [0174] In general, the first phase-transfer agent in step a) can be in any amount suitable for the reaction. In some embodiments, in step a), the first phase-transfer agent is present in an amount of no more than about 50%, about 40%, less than about 30%, about 20%, or about 10% by weight, based on buprenorphine or the salt thereof. In some embodiments, in step a), the first phase-transfer agent (e.g., tetrabutylammonium hydroxide) is present in an amount of no more 25 than about 10% by weight, based on buprenorphine or the salt thereof. In some embodiments, in

step a), tetrabutylammonium hydroxide is present in an amount of no more than about 10% by weight, based on buprenorphine or the salt thereof. In some embodiments, in step a), tetrabutylammonium hydroxide is present in an amount of from about 2% to about 10% by weight, based on buprenorphine or the salt thereof. In some embodiments, in step a),

5 tetrabutylammonium hydroxide is present in an amount of from about 3% to about 8% by weight, based on buprenorphine or the salt thereof. In some embodiments, in step a), tetrabutylammonium hydroxide is present in an amount of about 5% by weight, based on buprenorphine or the salt thereof.

[0175] In general, the second phase-transfer agent in step b) can be in any amount suitable for the reaction. In some embodiments, in step b), the second phase-transfer agent is present in a

10 substoichiometric amount (e.g., less than 1 equivalent), relative to the compound of formula (II). In some embodiments, in step b), the second phase-transfer agent (e.g., tetrabutylammonium hydroxide) is present in an amount of no more than about 0.5 equivalents, relative to the compound of formula (II). In some embodiments, in step b), tetrabutylammonium hydroxide is

15 present in an amount of no more than about 0.5 equivalents, relative to the compound of formula (II). In some embodiments, in step b), tetrabutylammonium hydroxide is present in an amount of from about 0.2 to about 0.5 equivalents, relative to the compound of formula (II). In some embodiments, in step b), tetrabutylammonium hydroxide is present in an amount of about 0.3 equivalents, relative to the compound of formula (II).

20 [0176] In general, in step b), the buprenorphine or the salt thereof can be present in any amount suitable for the reaction. In some embodiments, the buprenorphine or the salt thereof is present in a substoichiometric amount (e.g., less than 1 equivalent), relative to the compound of formula (II). In some embodiments, in step b), buprenorphine or the salt thereof is present in an amount of from about 0.8 to about 1.0 equivalents, relative to the compound of formula (II). In

25 some embodiments, in step b), buprenorphine or the salt thereof is present in an amount of about 0.9 equivalents, relative to the compound of formula (II). In some embodiments, in step b), buprenorphine or the salt thereof is present in an amount of about 0.8 equivalents, relative to the compound of formula (II).

[0177] In general, in step b), the aprotic solvent can be any aprotic solvent suitable for the

30 reaction. In some embodiments, in step b), the aprotic solvent is toluene.

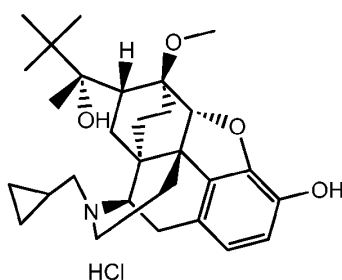
[0178] In general, steps a) and b) can be conducted at any suitable temperature. In some embodiments, steps a) and b) are each conducted at an elevated temperature (e.g., above room temperature). In some embodiments, step a) is conducted at a temperature of from about 40°C to about 80°C. In some embodiments, step a) is conducted at a temperature of from about 50°C to about 70°C. In some embodiments, step a) is conducted at a temperature of about 60°C. In some embodiments, step b) is conducted at a temperature of from about 60°C to about 110°C. In some embodiments, step b) is conducted at a temperature of from about 70°C to about 100°C. In some embodiments, step b) is conducted at a temperature of about 85°C.

[0179] In general, the compound of formula (II) obtained from step a) can be used in step b) with or without purification. In some embodiments, the compound of formula (II) obtained from step a) is used directly in step b). In some embodiments, the compound of formula (II) obtained from step a) is used directly in step b) without purification.

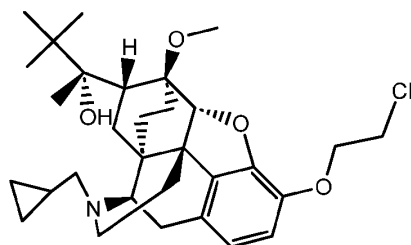
[0180] In general, the buprenorphine dimer of formula (I) in a neutral form can be further purified by a standard purification method (e.g., chromatography, extraction, recrystallization, etc.). In some embodiments, the buprenorphine dimer of formula (I) in a neutral form is further purified by trituration in an organic solvent. In some embodiments, the buprenorphine dimer of formula (I) in a neutral form is further purified by trituration in acetone.

[0181] In a fourth aspect, the present disclosure provides a process preparing a buprenorphine dimer in a neutral form, represented by formula (I), the process including:

a) combining a buprenorphine HCl salt, represented by the formula:



an aqueous NaOH solution, and tetrabutylammonium hydroxide in 1,2-dichloroethane to form a compound of formula (II):



(II); and

b) combining the compound of formula (II), a buprenorphine HCl salt, an aqueous NaOH solution, and tetrabutylammonium hydroxide in toluene to provide the buprenorphine dimer of formula (I) in a neutral form.

5 [0182] Reaction conditions of steps a) and b) are each described above in the third aspect.

[0183] In some embodiments, in each of steps a) and b), the aqueous NaOH solution is a 25% NaOH aqueous solution. In some embodiments, in step a), tetrabutylammonium hydroxide is present in an amount of about 5% by weight, based on the buprenorphine HCl salt. In some
10 embodiments, in step b), tetrabutylammonium hydroxide is present in an amount of about 0.3 equivalents, relative to the compound of formula (II). In some embodiments, in step b), buprenorphine or the salt thereof is present in an amount of about 0.8 equivalents, relative to the compound of formula (II). In some embodiments, step a) is conducted at a temperature of about 60°C. In some embodiments, step b) is conducted at a temperature of about 85°C. In some
15 embodiments, the compound of formula (II) obtained from step a) is used directly in step b) without purification. In some embodiments, the buprenorphine dimer of formula (I) in a neutral form is further purified by trituration in acetone.

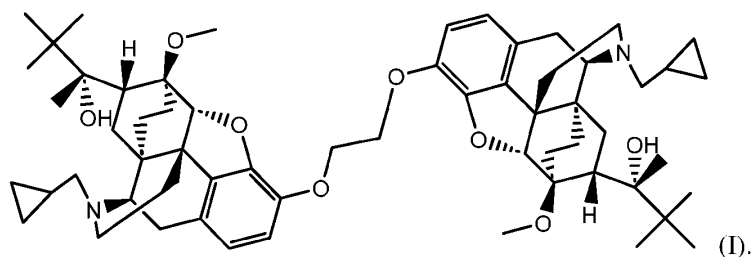
[0184] In some embodiments, the compound of formula (II) is obtained from step a) in a yield of at least 95% yield. In some embodiments, the compound of formula (II) is obtained from step a) in a quantitative yield.

20 [0185] In some embodiments, the buprenorphine dimer of formula (I) in a neutral form is obtained in a yield of at least 80% in two steps (i.e., steps a) and b)). In some embodiments, the buprenorphine dimer of formula (I) in a neutral form is obtained in a yield of at least 80% in two steps (i.e., steps a) and b)) with a purity of at least 95%.

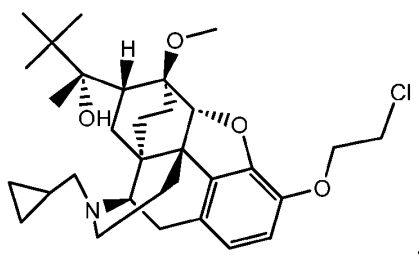
[0186] In some embodiments, after purification (e.g., trituration in acetone), the buprenorphine dimer of formula (I) in a neutral form is isolated in a purity of at least 99%.

V. COMPOUNDS

[0187] In one aspect, the present disclosure provides a buprenorphine dimer in a neutral form,
5 represented by formula (I):



[0188] In another aspect, the present disclosure provides a compound, represented by formula
(II):

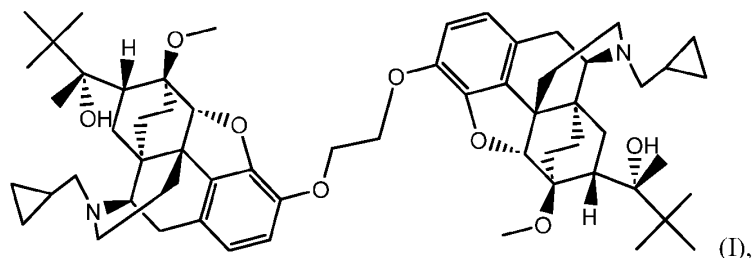


10 or a salt thereof.

[0189] In some embodiments, the compound of formula (II) is in a neutral form.

VI. ENUMERATED EMBODIMENTS

1. A method of treating a disease in a human subject in need thereof,
15 comprising orally administering to the subject a therapeutically effective amount of a
buprenorphine dimer represented by formula (I):



or a pharmaceutically acceptable salt thereof, wherein

the therapeutically effective amount of the buprenorphine dimer is a total daily dose of at least about 100 mg per day on a salt-free and anhydrous basis; and

5 the administering achieves a plasma concentration of at least about 700 ng/mL in the subject.

2. The method of embodiment 1, wherein the buprenorphine dimer is in a neutral form, represented by formula (I).

3. The method of embodiment 1 or 2, wherein the therapeutically effective
10 amount of the buprenorphine dimer is a total daily dose of at least about 200 mg per day on a salt-free and anhydrous basis.

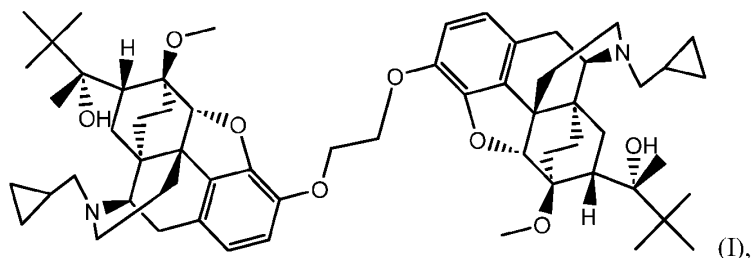
4. The method any one of embodiments 1-3, wherein the buprenorphine dimer is administered once daily.

5. The method of any one of embodiments 1-3, wherein the buprenorphine
15 dimer is administered twice daily.

6. The method of any one of embodiments 1-5, wherein the disease is chronic pain.

7. The method of any one of embodiments 1-5, wherein the disease is Irritable Bowel Syndrome with Diarrhea (IBS-D).

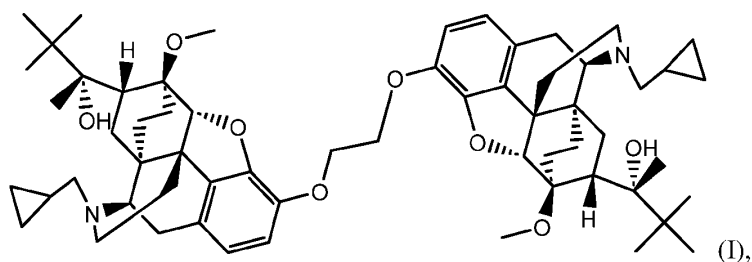
8. A method of treating a chronic pain in a subject in need thereof,
20 comprising administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



or a pharmaceutically acceptable salt thereof, wherein the buprenorphine dimer is administered orally.

9. The method of embodiment 8, wherein the buprenorphine dimer is in a neutral form, represented by formula (I).

10. A method of treating a chronic pain in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a buprenorphine dimer in a neutral form represented by formula (I):



wherein the pharmaceutical composition is administered orally.

11. The method of any one of embodiments 8 to 10, wherein the chronic pain is a nociceptive pain, a neuropathic pain, or a combination thereof.

12. The method of any one of embodiments 8 to 11, wherein the chronic pain is a peripheral chronic pain.

13. The method of any one of embodiments 8 to 12, wherein the chronic pain is peripheral neuropathic pain.

14. The method of any one of embodiments **8** to **13**, wherein the subject has a sickle cell disease (SCD), cancer and/or under chemotherapy, HIV, diabetes, shingles, a traumatic injury, a surgery, an amputation, a burn, or a combination thereof; and/or the subject has or had a coronavirus disease.

- 5 **15.** The method of any one of embodiments **8** to **14**, wherein the chronic pain is any one of 1) to 10):
- 1) associated with a sickle cell disease (SCD) in the subject;
 - 2) a chemotherapeutic induced neuropathic pain in the subject who has cancer and under chemotherapy;
 - 10 3) HIV sensory neuropathy;
 - 4) a diabetic neuropathy pain;
 - 5) a post-herpetic neuralgia in the subject who has or had shingles;
 - 6) a post-trauma chronic pain;
 - 7) a post-surgical pain;
 - 15 8) a post-amputation pain;
 - 9) a post-burn pain; and
 - 10) associated with a long-term effect in the subject who had a coronavirus disease.

16. The method of any one of embodiments **8** to **15**, wherein the therapeutically effective amount is a total daily dosage of from about 50 mg to about 800 mg, 20 from about 50 mg to about 700 mg, from about 50 mg to about 600 mg, from about 50 mg to about 500 mg, from about 50 mg to about 400 mg, from about 50 mg to about 300 mg, or from about 50 mg to about 250 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

17. The method of embodiment **16**, wherein the therapeutically effective amount is a total daily dosage of about 100 mg of the buprenorphine dimer on a salt-free and 25 anhydrous basis.

18. The method of embodiment **16**, wherein the therapeutically effective amount is a total daily dosage of about 200 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

19. The method of any one of embodiments 8 to 18, wherein the buprenorphine dimer is administered once, twice, three times, or four times daily.

20. The method of embodiment 19, wherein the buprenorphine dimer is administered once daily.

5 21. The method of embodiment 19, wherein the buprenorphine dimer is administered twice daily.

22. The method of any one of embodiments 10 to 21, wherein the pharmaceutical composition comprising the buprenorphine dimer is a tablet.

10 23. The method of embodiment 22, wherein the tablet comprising buprenorphine dimer is an immediate-release tablet.

24. The method of any one of embodiments 8 to 23, wherein the therapeutically effective amount of the buprenorphine dimer reduces the chronic pain, measured by one or more criteria selected from the group consisting of:

- 1) a reduced monthly average score on a 0-10 Likert scale over past 1, 3, or 6 months,
15 relative to a monthly average score prior to the treating;
- 2) a reduced monthly average score of characteristic pain intensity and/or disability over past 1, 3, or 6 months, relative to a monthly average score prior to the treating; and
- 3) a reduced pain severity over past 1, 3, or 6 months relative to a pain severity prior to the treating, wherein the reduced pain severity is selected from the group consisting of:
20 i) from Grade 4 (high disability-severely limiting) to any one of Grade 3 (high disability-moderately limiting), Grade 2 (low disability-high intensity), Grade 1 (low disability-low intensity), and Grade 0 (no pain);
ii) from Grade 3 to any one of Grade 2, Grade 1, and Grade 0;
iii) from Grade 2 to Grade 1 or Grade 0; and
25 iv) from Grade 1 to Grade 0.

25. The method of any one of embodiments 8 to 24, wherein the therapeutically effective amount of the buprenorphine dimer provides an antihyperalgesic effect.

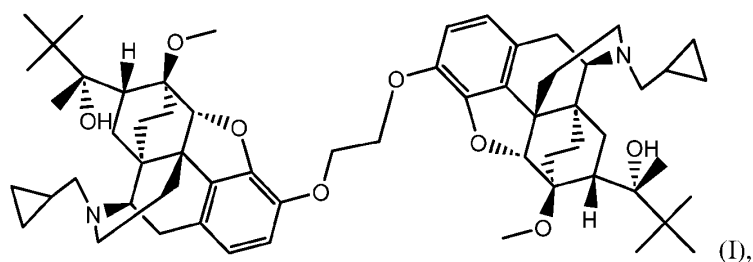
26. The method of any one of embodiments 8 to 25, wherein, during or after the treating, the subject has reduced hyperalgesia or is substantially free of hyperalgesia.

27. The method of embodiment 26, wherein, during or after the treating, the subject is free of hyperalgesia.

5 28. The method of any one of embodiments 8 to 27, wherein the subject is human.

29. The method of embodiment 28, wherein the human is an adult in an age of at least 18 years old.

30. A method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



or a pharmaceutically acceptable salt thereof, wherein the subject has 7 α -hydroxy-4-cholesten-3-one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

15 31. The method of embodiment 30, wherein the buprenorphine dimer is in a neutral form, represented by formula (I).

32. A method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a buprenorphine dimer in a neutral form represented by formula (I), wherein the subject has 7 α -hydroxy-4-cholesten-3-one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

33. The method of any one of embodiments 30 to 32, wherein the buprenorphine dimer has the name of (2S,2'S)-2,2'-((4R,4aS,4'R,4a'S,6R,6'R,7R,7aR,7'R,7a'R,12bS,12b'S)-(ethane-1,2-diylbis(oxy))bis(3-(cyclopropylmethyl)-7-methoxy-1,2,3,4,5,6,7,7a-octahydro-4a,7-ethano-4,12-methanobenzofuro[3,2-c]isoquinoline-9,6-diyl))bis(3,3-dimethylbutan-2-ol).
34. The method of any one of embodiments 30 to 32, wherein the subject has a C4 level of from about 15 mg/dL to about 45 mg/dL in blood.
35. The method of any one of embodiments 30 to 34, wherein, prior to the treating, the subject has worst abdominal pain over past 24 hours in a weekly average score of more than 3, based on a 1-10 numeric rating scale.
36. The method of any one of embodiments 30 to 35, wherein, prior to the treating, the subject has stool consistency in a weekly average score of greater than 5, as assessed via Bristol Stool Form Score (BSFS).
37. The method of any one of embodiments 30 to 36, wherein the subject has cholecystectomy.
38. The method of any one of embodiments 30 to 37, wherein, during the treating, the subject receives loperamide.
39. The method of any one of embodiments 30 to 38, wherein, during the treating, the subject receives loperamide in a total dosage of no more than any one of 8 mg over 24 hours, 14 mg over 48 hours, and 22 mg over 7 days.
40. The method of any one of embodiments 30 to 37, wherein, during the treating, the subject does not receive loperamide.
41. The method of any one of embodiments 30 to 40, wherein the therapeutically effective amount is a total daily dosage of from about 50 mg to about 250 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

42. The method of embodiment **41**, wherein the therapeutically effective amount is a total daily dosage of about 100 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

43. The method of any one of embodiments 30 to **42**, wherein the
5 buprenorphine dimer is administered orally.

44. The method of any one of embodiments 30 to **43**, wherein the buprenorphine dimer is administered once, twice, three times, or four times daily.

45. The method of embodiment **44**, wherein the buprenorphine dimer is administered once daily.

10 **46.** The method of embodiment **45**, wherein the buprenorphine dimer is administered at least about 30 minutes prior to breakfast.

47. The method of any one of embodiments **32** to **46**, wherein the pharmaceutical composition comprising the buprenorphine dimer is a tablet.

48. The method of embodiment **47**, wherein the tablet comprising
15 buprenorphine dimer is an immediate-release tablet.

49. The method of any one of embodiments 30 to 48, wherein the subject is treated for a period of at least 12 weeks.

50. The method of any one of embodiments 30 to **49**, wherein the therapeutically effective amount of the buprenorphine dimer reduces one or more symptoms
20 associated with IBS-D.

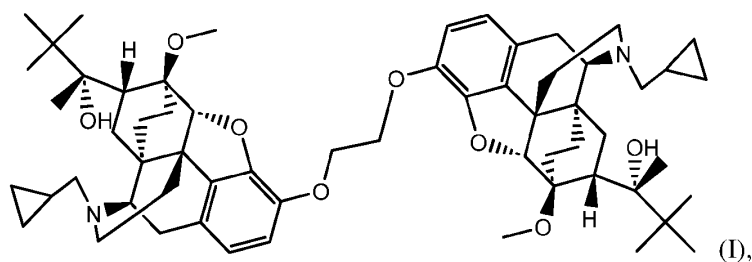
51. The method of embodiment **50**, wherein the therapeutically effective amount of the buprenorphine dimer

- 1) reduces a weekly average score of worst abdominal pain over past 24 hours by at least 30%, relative to the weekly average score prior to the treating; and/or
- 25 2) improves stool consistency, measured by i) a reduced average BSFS score to less than 6, or ii) an absence of a bowel movement provided that features of 1) are met.

52. The method of any one of embodiments **30** to **51**, wherein the subject is human.

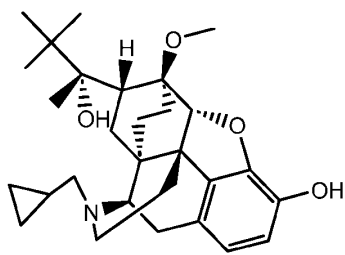
53. The method of embodiment **52**, wherein the human is an adult in an age of at least 18 years old.

54. A process for preparing a buprenorphine dimer in a neutral form, represented by formula (I):

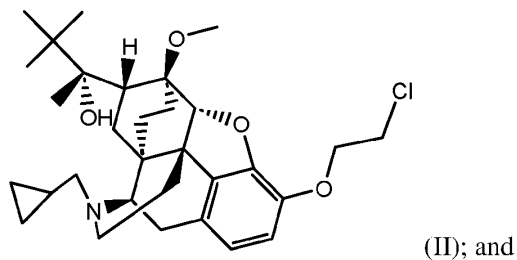


comprising:

a) combining buprenorphine or a salt thereof, represented by the formula:



a first inorganic base, water, and a first phase-transfer agent in 1,2-dichloroethane to form a compound of formula (II):



b) combining the compound of formula (II), buprenorphine or a salt thereof, a second inorganic base, water, and a second phase-transfer agent in an aprotic solvent to provide the buprenorphine dimer of formula (I) in a neutral form.

55. The process of embodiment **54**, wherein the buprenorphine in steps a) and b) are each a buprenorphine HCl salt.

56. The process of embodiment **54** or **55**, wherein the first and second inorganic bases are each an alkali hydroxide independently selected from the group consisting of
5 LiOH, NaOH, KOH, and CsOH.

57. The process of embodiment **56**, wherein the first and second inorganic bases are each NaOH.

58. The process of embodiment **56** or **57**, wherein the first and second inorganic bases together with the water are each an aqueous NaOH solution.

10 **59.** The process of any one of embodiments **54** to **58**, wherein the first and second phase-transfer agents are each independently a quaternary ammonium salt.

60. The process of embodiment **59**, wherein the first and second phase-transfer agents are each tetrabutylammonium hydroxide.

15 **61.** The process of embodiment **60**, wherein, in step a), tetrabutylammonium hydroxide is present in an amount of about 5% by weight, based on buprenorphine or the salt thereof; and/or in step b), tetrabutylammonium hydroxide is present in an amount of about 0.3 equivalents, relative to the compound of formula (II).

62. The process of any one of embodiments **54** to **61**, wherein, in step b), buprenorphine or the salt thereof is present in an amount of about 0.8 equivalents, relative to the
20 compound of formula (II).

63. The process of any one of embodiments **54** to **62**, wherein, in step b), the aprotic solvent is toluene.

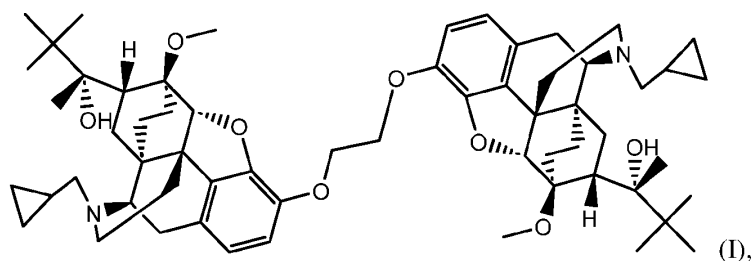
64. The process of any one of embodiments **54** to **63**, wherein step a) is conducted at a temperature of from about 50°C to about 70°C; and/or step b) is conducted at a
25 temperature of from about 70°C to about 100°C.

65. The process of embodiment **64**, wherein step a) is conducted at a temperature of about 60°C; and/or step b) is conducted at a temperature of from about 85°C.

66. The process of any one of embodiments **54** to **65**, wherein the compound of formula (II) obtained from step a) is used directly in step b) without purification.

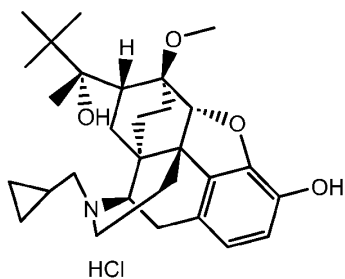
5 **67.** The process of any one of embodiments **54** to **66**, wherein the buprenorphine dimer of formula (I) in a neutral form is further purified by trituration in acetone.

68. A process for preparing a buprenorphine dimer in a neutral form, represented by formula (I):

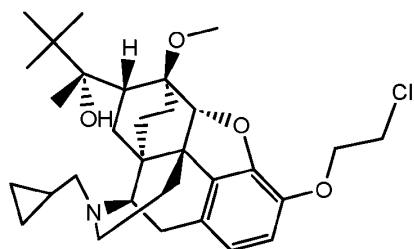


10 comprising:

a) combining a HCl salt of buprenorphine, represented by the formula:



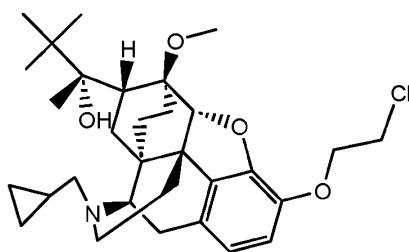
an aqueous NaOH solution, and tetrabutylammonium hydroxide in 1,2-dichloroethane to form a compound of formula (II):



(II); and

b) combining the compound of formula (II), a HCl salt of buprenorphine, an aqueous NaOH solution, and tetrabutylammonium hydroxide in toluene to provide the buprenorphine dimer of formula (I) in a neutral form.

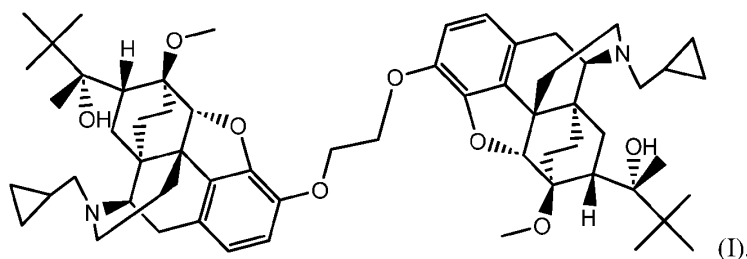
5 **69.** A compound, represented by formula (II):



or a salt thereof.

70. The compound of embodiment **69**, in a neutral form.

10 **71.** A method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a buprenorphine dimer represented by formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein the subject has had a cholecystectomy prior to the administering.

15

VII. EXAMPLES

Example 1: Study of Spinal Nerve Ligation Induced Neuropathic Pain in the Rat (Chugn Model)

5 [0190] The buprenorphine dimer HCl was dissolved in dimethyl sulfoxide (DMSO)/Solutol HS-15/Phosphate buffered saline (PBS) (5/5/90) and administered subcutaneously, intraperitoneally, or intravenously at the dosing volume of 5 or 10 mL/kg.

[0191] A cohort of 30 male Sprague-Dawley (SD) rats, weighing 180 – 220 g at arrival, was housed under constant temperature, humidity and a 12-hour light-dark cycle. Following acclimation to the animal colony, the animals were tested for baseline withdrawal responses to
10 mechanical allodynia (von Frey filaments) using the methods described as the followings. The animals were anesthetized with Pentobarbital (50 mg/kg, IP). The left paraspinal muscles were separated from the spinous processes (L4 – S2). The L6-S1 facet joint was nipped. The transverse process of L6 was removed to identify the locations of the L5 and L6 spinal nerve. The left L5 and L6 spinal nerves were isolated and tightly ligated with 6.0 silk sutures.

15 [0192] The animals were tested for pre-dose mechanical allodynia by the manual von Frey test (Chaplan up/down method using von Frey filaments on the plantar surface of the left hind paw) 13, 21 or 37 days after the surgery. The animals were randomized into the vehicle and treatment groups based on mechanical allodynia scores.

[0193] Mechanical allodynia was performed 1 and 3 hours after dosing of vehicle or test
20 articles on Day 14, Day 22 or Day 38, as shown in **FIG. 1**. The animals had free access to food and water until being tested. The animals were placed under inverted plastic cages on a wire mesh rack and allowed to acclimate for 20 to 30 minutes. Allodynia was evaluated using the Chaplin “up/down” method using von Frey hairs. The applied force-filaments were magnitude 3.61 (0.4 g), 3.84 (0.6 g), 4.08 (1.0 g), 4.31 (2.0 g), 4.56 (4.0 g), 4.74 (6.0 g), 4.93 (8.0 g), and
25 5.18 (15.0 g).

[0194] The mechanical allodynia test started with the monofilament handle marked 4.31 (2.0 g), applying the nylon filament beneath the wire mesh perpendicularly to the plantar surface of the appropriate left hind paw. This step was repeated 3 to 5 times in succession covering a broad plantar area of the same animal until a response was observed. Brisk withdrawal or paw

flinching was considered a positive response and thereafter a weaker monofilament was chosen and applied in the same manner as previously described. Static movement of the paw (excluding locomotion) was considered a negative response and thereafter a stronger monofilament was applied in the same manner.

5 [0195] **Mechanical Allodynia (Study 1/Day 14):** Buprenorphine dimer of formula (I) HCl, morphine, and the vehicle were administered intraperitoneally or subcutaneously to groups of 10 SD rats on Day 14 after SNL. Mechanical allodynia was evaluated 1 and 3 hr after dosing. One-way ANOVA followed by Dunnett's test was applied for comparison between the vehicle control and test compound treated groups. **FIG. 2** shows the results. *P<0.05, treated vs.
10 vehicle control.

[0196] **Mechanical Allodynia (Study 2/Day 22):** Buprenorphine dimer of formula (I) HCl, morphine, buprenorphine and the vehicle were administered subcutaneously, intraperitoneally or intravenously to groups of 3 - 5 SD rats on Day 22 after SNL. Mechanical allodynia was evaluated 1 and 3 hr after dosing. One-way ANOVA followed by Dunnett's test was applied for
15 comparison between the vehicle control and test compound treated groups. **FIG. 3** shows the results. *P<0.05, treated vs. vehicle control.

[0197] **Mechanical Allodynia (Study 3/Day 38):** Buprenorphine dimer of formula (I) HCl, buprenorphine, gabapentin and the vehicle were administered orally or subcutaneously to groups of 2 - 5 SD rats on Day 38 after SNL. Mechanical allodynia was evaluated 1 and 3 hr after
20 dosing. One-way ANOVA followed by Dunnett's test was applied for comparison between the vehicle control and test compound treated groups. **FIG. 4** shows the results. *P<0.05, treated vs. vehicle control.

[0198] Buprenorphine dimer, administered subcutaneously 100 mg/kg and 200 mg/kg (488 mg and 976 mg HED in a 60-kg human, respectively), elicited statistically significant reduction in
25 hyperalgesia at 3 hours. The effect was comparable to that of oral gabapentin 100 mg/kg.

[0199] In conclusion, results from the Chung study suggest that the minimum threshold plasma levels necessary for elucidating anti-nociceptive effect is about 729 ng/mL of buprenorphine dimer.

Example 2: Antihyperalgesic Effect of Buprenorphine Dimer in Mouse Models

[0200] Prior to investigating the antihyperalgesic effect of Buprenorphine dimer in the mouse model as described herein, it was important to establish that the model would be sensitive enough to discriminate hyperalgesic pain (sensitized state) from mechanical non-hyperalgesic pain (non-sensitized state). The first part of this study was conducted following oral administration of a single dose of buprenorphine dimer vs. saline control at a fixed colorectal balloon pressure (30 mmHg).

[0201] As shown in **FIG. 5A**, in normal mice experiencing mechanical pain, there were small differences between the vehicle and the dimer treated groups. In the sensitized group (**FIG. 5B**), there was a large and statistically significant difference between the vehicle control and the dimer treatment groups, confirming a clear antihyperalgesic response after a single dose.

[0202] In the second experiment (**FIG. 6**), the effects of Buprenorphine dimer (50 mg/kg) vs. oral eluxadoline (50 mg/kg), both administered orally, were compared using increasing distension pressures after daily dosing for 5 days. There was a significant difference between the visceromotor response of Buprenorphine dimer and eluxadoline, confirming antihyperalgesic effects of Buprenorphine dimer. For Buprenorphine dimer, the curve shifted downward ($p=0.001$, two-way ANOVA), indicating a potent antihyperalgesic effect. Eluxadoline did not demonstrate antihyperalgesic effects, in that its effect was no different from that of placebo.

[0203] Subsequently, the antihyperalgesic effect of orally administered Buprenorphine dimer at lower doses was investigated, as described in **FIG. 7**. The results confirmed that Buprenorphine dimer mitigated visceral pain induced by distension of a colorectal balloon at all investigated doses, i.e., 1 to 15 mg/kg. The human equivalent doses tested in this study include doses in the range of 5 to 50 mg, which are expected to be effective in moderating gastrointestinal hypermotility.

Example 3: Phase 1 Clinical Study in Healthy Subjects

[0204] Buprenorphine dimer of formula (I) (in a neutral form) was absorbed after oral doses in healthy normal volunteers. All doses investigated were safe and well tolerated.

[0205] The single ascending dose (SAD) study evaluated the safety, pharmacodynamics, and pharmacokinetics of oral Buprenorphine dimer at six dose levels. These doses were 5, 15, 50, 150, 400, and 800 mg, and were administered after overnight fasting. Buprenorphine dimer plasma concentrations were measured out to 72 hours. The median T_{max} was 8 hours at all dose levels (range from 4 to 12 hours). The half-life was consistent across all doses, between 21 to 27 hours. The pharmacokinetics of oral Buprenorphine dimer after a single dose was dose dependent and nonlinear, as illustrated in **FIG. 8A** and **FIG. 8B**. **Table 1** shows summary of plasma concentrations of buprenorphine dimer (ng/mL) at selected doses and time points.

Table 1: Summary of Plasma Concentrations of Buprenorphine Dimer (ng/mL)

Time point	Buprenorphine Dimer Dose			
	50 mg	150 mg	400 mg	800 mg
	Maximum Plasma Concentration (ng/mL)			
Hour 4	140.6	2576.3	915.8	574.628
Hour 8	419.6	2073.4	2130.3	1198.7
Hour 12	316.4	1518.0	2648.9	996.5

[0206] The multiple ascending dose (MAD) study evaluated the safety, pharmacodynamics, and pharmacokinetics of oral buprenorphine dimer at six dose levels. These doses were 5, 15, 50, 100, 150, and 400 mg, and they were administered daily for 7 days after overnight fasting. Serial blood samples were drawn for plasma assay of buprenorphine dimer on days 1 and 7. Additionally, samples were collected for trough concentrations on days 4 through 6. The median T_{max} was about 6 hours at all dose levels (ranging from 1 to 8 hours) and the mean half-life on day 7, based on plasma levels over 96 hours, was between 36 to 43 hours. Statistical analyses indicated that Buprenorphine dimer steady state was reached by day 5 at all doses and the steady-state plasma exposure levels (C_{max} and AUC_{0-24h}) in general were approximately 2.5 times the level on day 1 (accumulation factor 2.6). The steady-state pharmacokinetics of oral buprenorphine dimer after daily administration was also dose dependent and nonlinear, as illustrated in **FIG. 9A** and **FIG. 9B**. **Table 2** shows summary of plasma concentrations of Buprenorphine dimer (ng/mL) at selected doses and time points.

Table 2: Summary of Plasma Concentrations of Buprenorphine Dimer (ng/mL)

Time point	Buprenorphine Dimer Dose			
	50 mg	100 mg	150 mg	400 mg
	Mean Plasma Concentration (ng/mL)			
Day 7, 3 hr	122.6	810.3	622.3	754.1
Day 7, 4 hr	173.1	919.9	710.2	1025.6
Day 7, 5 hr	286.6	1350.4	1022.3	1510.2
Day 7, 5.5 hr	367.9	1308.3	1124.3	1701.7
Day 7, 6 hr	351.5	1262.1	1119.1	1613.4
Day 7, 6.5 hr	358.4	1219.5	1170.8	1719.1
Day 7, 7 hr	333.8	1157.3	1190.3	1630.2
Day 7, 7.5 hr	364.3	1077.7	1212.6	1456.3
Day 7, 8 hr	298.6	1053.9	1211.9	1440.4
Day 7, 10 hr	314.5	892.3	1075.0	1238.4
Day 7, 12 hr	248.2	791.3	976.0	1032.5
	Maximum Plasma Concentration (ng/mL)			
Day 7, 5 hr	799.6	2001.1	2059.8	2829.0
Day 7, 5.5 hr	1161.3	1814.1	2086.2	3395.8
Day 7, 6 hr	1055.0	1789.9	2191.2	3087.2
Day 7, 6.5 hr	1060.2	1692.8	2332.4	3551.8
Day 7, 7 hr	976.6	1632.3	2404.3	3024.7
Day 7, 7.5 hr	1147.9	1474.3	2239.4	2616.2
Day 7, 8 hr	893.2	1616.5	2384.8	2844.8
Day 7, 10 hr	981.2	1404.7	2108.3	2261.8
Day 7, 12 hr	677.2	1286.1	1986.1	1904.0

[0207] Surprisingly and unexpectedly, in humans, the buprenorphine dimer of formula (I) in a neutral form (i.e., free base) is rapidly absorbed affording blood levels of as high as 2000 to 3000 ng/mL. See **Table 1** and **Table 2**. From MAD mean plasma concentrations, on Day 7, the mean

plasma concentration of buprenorphine dimer of formula (I) was achieved at a steady-state level of above 700 ng/mL, when dosed at 100 mg per day. See FIG. 9C.

Example 4: Dose Rational for Treating Peripheral Chronic Pain in a Subject having a Sickle Cell Disease

5 [0208] Results from the clinical PK studies in healthy volunteers indicate that a minimum of 100 mg dose (e.g., a 100 mg dose once or twice daily) would be necessary to achieve the threshold plasma concentration of 700 ng/mL for any anti-nociceptive effect in patients. The data also suggests that the concentrations are highly variable and the mean levels drop below 700 ng/mL about 18 hours post-dose. It has also been reported (communications with Dr. K. Gupta)

10 that the renal clearance in sickle cell disease patients is generally greater than in healthy volunteers. The data from the healthy volunteer study suggests that renal clearance is not the major route of elimination for buprenorphine dimer. To minimize healthy volunteer-to-patient variability and to sustain drug exposure above 700 ng/mL, buprenorphine dimer 200 mg twice daily, to be administered 30 minutes before meals will be investigated in a Phase 2 chronic

15 efficacy study in patients with sickle cell disease.

Example 5: Whole Body Autoradiography Study

[0209] Following oral administration of approximately 100 mg/kg of ^{14}C -labelled buprenorphine dimer to intact male rats, limited distribution of drug-derived radioactivity was observed. The limit of quantitation (LOQ) was determined to be approximately 1,174

20 nanogram-equivalents of ^{14}C -labelled buprenorphine dimer per gram of tissue. A total of 45 different tissues were quantitated. The majority of the tissues noted as strongly positive were part of the gastrointestinal tract and associated organ systems. For the few tissues noted as positive, they were cleared from the body relatively quickly. Only two tissues were noted as positive (slightly above the LOQ) at 168 hours after administering: Spleen and Adrenal gland.

25 [0210] For intact male rats, the $C_{\max}$ for distribution for most tissues was observed at the 2 hour time point, the earliest time point analyzed, and 11 of 45 tissues were noted as positive. **Table 3** lists the observed concentration of ^{14}C -labelled buprenorphine dimer (ng-cq/g) in various tissues.

Table 3: Concentration of ^{14}C -labelled Buprenorphine Dimer (ng-eq/g) in Various Tissues by Whole Body Autoradiography

Tissue	Time Point				
	2 hr	8 hr	24 hr	48 hr	168 hr
Adrenal gland	2709	4737	4152	4211	1978
Blood	1262	BLQ	BLQ	BLQ	BLQ
Bone	ND	ND	ND	ND	ND
Bone marrow	BLQ	1424	BLQ	1344	BLQ
Cecum	BLQ	BLQ	BLQ	BLQ	BLQ
Cecum contents	4474873	530551	39950	12688	BLQ
Cerebellum	ND	ND	ND	ND	ND
Cerebrum	ND	ND	ND	ND	ND
Epididymis	ND	ND	ND	ND	ND
Esophageal contents	12943	1979	2773	BLQ	BLQ
Ex-orbital lacrymal gland	BLQ	BLQ	BLQ	ND	ND
Eye	ND	ND	ND	ND	ND
Fat (brown)	BLQ	BLQ	BLQ	BLQ	BLQ
Fat (white)	ND	ND	ND	ND	ND
Harderian gland	BLQ	BLQ	BLQ	ND	ND
Intra-orbital lacrymal gland	ND	ND	ND	ND	ND
Kidney	BLQ	BLQ	BLQ	BLQ	BLQ
Large intestine	BLQ	BLQ	BLQ	BLQ	BLQ
Large intestinal contents	71832	1655177	116034	49355	BLQ
Liver	4735	5388	2840	2438	BLQ
Lung	BLQ	BLQ	BLQ	BLQ	BLQ
Lymph nodes	ND	ND	ND	ND	ND
Medulla	ND	ND	ND	ND	ND
Muscle	BLQ	BLQ	BLQ	BLQ	BLQ
Myocardium	BLQ	BLQ	BLQ	BLQ	BLQ
Nasal turbinates	ND	ND	ND	ND	ND

Tissue	Time Point				
	2 hr	8 hr	24 hr	48 hr	168 hr
Olfactory lobe	ND	ND	ND	ND	ND
Pancreas	ND	ND	ND	ND	ND
Pituitary gland	ND	ND	ND	ND	ND
Preputial gland	ND	ND	ND	ND	ND
Prostate gland	ND	ND	ND	ND	ND
Seminal vesicle	ND	ND	ND	ND	ND
Skin	BLQ	BLQ	BLQ	BLQ	BLQ
Small intestine	BLQ	BLQ	BLQ	BLQ	BLQ
Small intestinal contents	1232817	262976	11220	5675	ND
Spinal cord	ND	ND	ND	ND	ND
Spleen	2562	4743	2949	3687	2308
Stomach	BLQ	BLQ	BLQ	BLQ	BLQ
Stomach contents	1226432	498900	14810	1244	BLQ
Submaxillary gland	BLQ	BLQ	BLQ	BLQ	BLQ
Testes	ND	ND	ND	ND	ND
Thymus	ND	ND	ND	ND	ND
Thyroid gland	ND	ND	ND	ND	ND
Urine	2139	3975	NR	BLQ	BLQ

BLQ – Below limit of quantitation (<1174 ng-eq/g); and ND – Not detectable (sample shape not discernible from background or surrounding tissue)

[0211] The eleven tissues, listed from highest to lowest concentration, included: Cecum contents, Small intestinal contents, Stomach contents, Large intestinal contents, Esophageal contents, Liver, Adrenal gland, Spleen, Urine, Blood, and Bone marrow. Individual tissues noted as positive are described below.

[0212] **Cecum contents:** $C_{\max}$ of 4,474,873 ng-eq/g at 2 hours post-administration. Steady decrease in concentration observed through 48 hours post-administration, and below the LOQ at 168 hours post-administration.

[0213] **Small intestinal contents:** $C_{\max}$ of 1,232,817 ng-eq/g at 2 hours post-administration. Steady decrease in concentration observed through 48 hours post-administration, and not detected at 168 hours post-administration.

5 [0214] **Stomach contents:** $C_{\max}$ of 1,226,432 ng-eq/g at 2 hours post-administration. Steady decrease in concentration observed through 48 hours post-administration, and below the LOQ at 168 hours post-administration.

[0215] **Large intestinal contents:** $C_{\max}$ of 1,655,177 ng-eq/g at 8 hours post-administration. Steady decrease in concentration observed through 48 hours post-administration, and below the LOQ at 168 hours post-administration.

10 [0216] **Esophageal contents:** $C_{\max}$ of 12,943 ng-eq/g at 2 hours post-administration. Steady decrease in concentration observed through 24 hours post-administration, and below the LOQ at 48 and 168 hours post-administration.

[0217] **Liver:** $C_{\max}$ of 5,388 ng-eq/g at 8 hours post-administration. Steady decrease in concentration observed through 48 hours post-administration, and below the LOQ at 168 hours
15 post-administration.

[0218] **Adrenal gland:** $C_{\max}$ of 4,737 ng-eq/g at 8 hours post-administration. Plateau in concentration observed through 48 hours post-administration, with a decline observed at 168 hours post-administration.

Example 6: Absence of Buprenorphine Dimer in Brain, Spinal Cord, Pupillary

20 **Constriction, and Absence of Sign and Symptoms of Opioid Central Effects**

A. Brain and Spinal Cord in Rat

[0219] **Table 3** in Example 5 lists radioactivity in fluids and tissues after single oral dose of ^{14}C -labelled buprenorphine dimer. Radioactive dimer was not detected in the cerebellum, cerebrum, or spinal cord.

25 **B. Pupillometry Results in Human**

[0220] Pupillary Constriction was evaluated in both single ascending dose (SAD) and multiple ascending dose (MAD) studies of Phase 1 Clinical Study (as described in Example 4).

[0221] **SAD Study:** No subject was reported to have pinpoint pupils (< 2 mm) pre or post dosing. Only one subject was observed with a pupillary diameter < 4 mm (3.9 mm at baseline) and this patient's pupillary diameter remained unchanged post dosing.

5 [0222] While statistically significant changes from baseline in pupil size were observed in the 5 mg, 150 mg and 400 mg cohorts, these post baseline changes are not believed to be clinically relevant and may represent inherent variability of the test.

[0223] **MAD study:** At pre-dose baseline, mean (SD) pupil diameter for buprenorphine dimer and placebo treated subjects were 6.393 (0.829) and 6.082 (0.663) mm respectively. On Day 7 at approximately 6 hours post dose, mean (SD) pupil diameter for buprenorphine dimer and
10 placebo treated subjects were 6.278 (0.764) and 6.271 (0.574) mm respectively.

[0224] There did not appear to be any trending dose response at post-dose time point for change in diameter from baseline for buprenorphine dimer treated subjects. There were no subjects with pupil diameter < or = to 4 mm in diameter at any time point during the study in any dosing group or placebo treated subjects. Overall there were no clinically relevant changes from
15 baseline in pupil diameter for any subject receiving buprenorphine dimer and no evidence for pinpoint (defined as diameter < or = to 2.0 mm) pupils post-dosing.

C. Absence of Sign and Symptoms of Opioid Central Effects in Human

[0225] A Double Blind, Placebo Controlled, Phase 2 Study of buprenorphine dimer has demonstrated that there are no clinical features suggestive of central nervous system effects by
20 the dimer.

D. Locomotor activity (LMA) and Pupil size in Rat

[0226] Buprenorphine dimer HCl administered intravenously (IV) at 50 mg/kg was assessed for potential adverse effects on locomotor activity (LMA) and pupil size, as compared to morphine at 5 mg/kg and eluxadoline at 50 mg/kg.

25 [0227] Groups of 4-6 Sprague-Dawley (SD) rats weighing 200 ± 20 g were employed. Buprenorphine dimer HCl and Eluxadoline were dissolved in vehicle DMSO/ Solutol® HS15/ PBS (5/5/90, v/v/v) and administered intravenously (IV) at 50 mg/kg, whereas morphine was injected at 5 mg/kg.

[0228] Immediately after test compound injection, the animals were placed individually into LMA chambers (Columbus Instruments, USA) in a quiet room at 25°C. For each 10-minute period over 60 min post dosing, individual motility counts (distance traveling, time spent traveling and vertical rearing) measured by interruption of infrared grids were totaled. The mean
5 $\pm$ SEM for each treatment group was then calculated. In addition, animals were observed for miosis immediately prior to and following LMS testing. One-way ANOVA followed by Dunnett's test was applied for comparison between vehicle and treated groups. Differences were considered significant at $P < 0.05$.

[0229] Individual total distance traveled (DT_{cm}) measured by interruption of infrared grids
10 was totaled every 10 min during the 60-min time period after dosing, as shown in **FIG. 10A**.
* $P < 0.05$, treated vs. vehicle control.

[0230] Individual total time spent traveled (ST_{sec}) measured by interruption of infrared grids was totaled every 10 min during the 60-min time period after dosing, as shown in **FIG. 10B**.
* $P < 0.05$, treated vs. vehicle control.

15 [0231] Individual total vertical reared (VC) measured by interruption of infrared grids was totaled every 10 min during the 60-min time period after dosing, as shown in **FIG. 10C**.
* $P < 0.05$, treated vs. vehicle control.

[0232] Buprenorphine dimer HCl exhibited a comparable activity in horizontal mobility counts (distance traveling and time spent traveling) and vertical counts (vertical rearing) over the 60
20 minute recording period, as compared to the vehicle control group (**FIGs. 10A-10C**). In contrast, morphine and eluxadoline significantly reduced both vertical and horizontal movements by more than 90%, signifying a severe sedative action. Consistent with the suppressive effect, eluxadoline at this dose level was associated with a 40% mortality within 3 hours post administration. However, no influences on pupil size were induced by treatments of
25 buprenorphine dimer HCl, morphine, and eluxadoline. Buprenorphine dimer HCl at 50 mg/kg was not associated with effects on locomotor activity and nor did it induce miosis.

Example 7: Stability of buprenorphine dimer of formula (I)

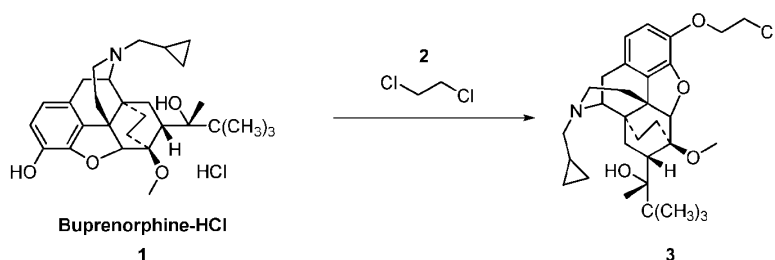
[0233] Buprenorphine dimer of formula (I) (1 mg/mL) was incubated for 30 minutes at room temperature and at 60°C in water (neutral), 1N HCl (acidic), and 5% NaHCO₃ (basic) condition

to assess the stability of the dimer. As shown in **FIG. 11**, buprenorphine dimer was found to be relatively stable, except for about 20% loss under the acidic condition at 60°C. The material formed during incubation in the acid at 60°C was a product of the dimer with a loss of methanol. No buprenorphine was detected.

- 5 **[0234]** To conclude, buprenorphine dimer of formula (I) does not hydrolyze to release buprenorphine or any other individual thebaine-derived molecules under neutral, acidic, and basic conditions, either at room or elevated temperatures. The only decomposition observed was loss of methanol after incubation under acidic conditions at 60°C. Results from these studies indicate that it is not possible to recover buprenorphine or individual thebaine-derived molecules
- 10 under various chemical or thermal conditions.

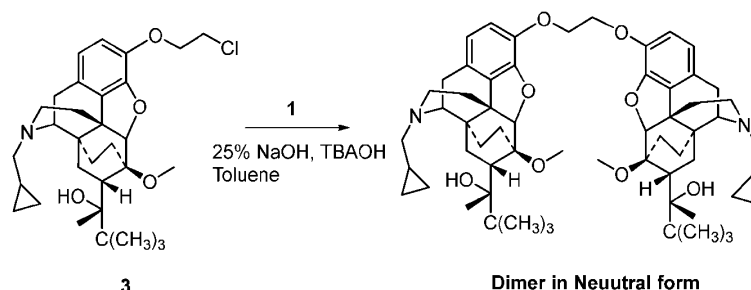
Example 8: Process for Preparing Buprenorphine Dimer in a Neutral Form

Step a)



- [0235]** Buprenorphine HCl (130 g), tetrabutylammonium hydroxide (TBAOH) (6.0 g, 5%),
- 15 25% aq. NaOH (1150 mL), and 1,2-dichloroethane (1380) were charged into a reaction vessel. The resulting mixture was heated to 60°C and held for 4 hr then checked for completion. Upon completion, the reaction mixture was cooled to room temperature and the phases were separated. The aqueous phase was then back extracted with methyl tert-butyl ether (MTBE) (1.5 L). The organic phases were combined and concentrated to dryness. The crude material (3) was used in
- 20 the next step without purification.

Step b)



[0236] Toluene (1.2 L) was charged to the container of crude intermediate (3) to form a homogenous solution, which was then charged to a 5-L 3-neck RBF equipped with mechanical stirring, thermal couple and condenser. Buprenorphine HCl (183.2 g, 0.8 eq. to step a)), TBAOH (72 g, 0.3 eq.), and 25% aq. NaOH (1.2 L) were charged to the reactor. The resulting mixture was heated to 85°C and held for at least 16 hr. Upon completion, the reaction mixture was cooled to room temperature and phases were separated. The aqueous phase was then back extracted with methyl tert-butyl ether (MTBE) (0.6 L). The combined organic phase was washed with brine (0.5 L) two times, then dried over Na₂SO₄, and filtered. The wet cake was washed with additional MTBE (0.5 L). The filtrates were collected and concentrated to about 782 g (about 3 vol), then charged with IPA (1.1 L, 5 vol) and then concentrated to about 787 g (about 3 vol), then charged with IPA (1.1 L) and concentrated to about 987 g (3-4 vol). The slurry was transferred to a flask then charged with IPA (1.1 L). The resulting mixture was then heated to reflux and held for 2 hr. The mixture was then cooled to 25°C and then filtered. The wet cake was washed with additional IPA (0.5 L) two times then dried at 50°C under vacuum to give 290 g of white solid (yield: 83%, purity: 98.9%).

[0237] **Purification by Trituration:** An increase in purity of crude dimer can be accomplished by trituration with 10 vols of acetone. Crude dimer (24 g, HPLC purity: 99.04%) was charged to acetone (0.24 L, 10 vol). The resulting mixture was heated to reflux and held for 3 hr then cooled to room temperature. Solids were filtered, and washed with acetone (50 mL, 2 vol) two times. Finally, the solids were dried at 50°C under vacuum to give 20 g of white solid (83%, HPLC purity: 99.48%).

[0238] Another batch of buprenorphine dimer in a neutral form was prepared according to the process as described above. Starting from buprenorphine HCl (275 g), buprenorphine dimer in a neutral form was isolated as white solid (300 g, yield: 80%, HPLC purity: 99.5%).

Example 9: A Double Blind, Placebo Controlled, Phase 2 Study – Protocol Summary

5 [0239] **Title:** A Double Blind, Placebo Controlled, Phase 2, Responsive Adaptive Randomization Study of Buprenorphine Dimer in Patients with Irritable Bowel Syndrome with Diarrhea (IBS D).

[0240] **Objectives:**

[0241] Primary Objective: Evaluate the efficacy of Buprenorphine Dimer in patients with IBS
10 D; and Evaluate the safety and tolerability of Buprenorphine Dimer in patients with IBS D.

[0242] Secondary Objectives: Assess changes in Quality of Life (QoL) during the treatment period.

[0243] **Methodology:**

[0244] This was a randomized, double-blind, placebo-controlled, 3-arm, 12-week, parallel
15 proof of concept study with 2 active arms (50 mg and 100 mg buprenorphine dimer) and 1 placebo arm, using a responsive adaptive randomization approach. After a 2-week screening period, patients who qualified entered the baseline symptom assessment period, which could last up to 3 weeks. Upon entering the baseline symptom assessment period, patients were instructed on completion of the eDiary for daily collection of data related to their IBS symptoms, bowel
20 function, and loperamide rescue usage (not allowed during baseline).

[0245] Patients who met all entry criteria were randomly assigned to receive one of two different doses of buprenorphine dimer tablets or placebo for 12 weeks. Study drug was to have been taken once daily (QD), approximately 30 minutes prior to breakfast. Patients returned to the clinic at Days 14, 28, 56, 84, and 2 weeks after dosing had been completed (Day 98) for a
25 follow-up visit. Patients who discontinued from the study prior to completion were to have returned to the study clinic as soon as possible after stopping study drug to complete early withdrawal procedures.

[0246] Patients continued to enter daily data related to their IBS symptoms, bowel function, and loperamide rescue use into the eDiary throughout the 12-week double-blind treatment period. Data from the eDiary entries were not provided to the investigator or site staff at any time during the study; however, the investigator received daily notifications related to patient
5 diary compliance, any episodes of diary recorded infrequent bowel movements (4 consecutive days with no bowel movement as confirmed by nonmissing diary entries), and excessive use of loperamide rescue for uncontrolled diarrhea. Patients were permitted to take loperamide 2 mg as needed every 6 hours, but were instructed not to exceed a total of 8 mg (4 tablets) in 24 hours, 14 mg (7 tablets) in 48 hours or 22 mg (11 tablets) over a 7-day period. Use above these amounts
10 was considered to be excessive and was flagged for investigator follow-up. The investigator was to have contacted the patient for an assessment and/or an unscheduled visit as soon as possible in response to a notification of excessive loperamide use or a notification of diary recorded infrequent bowel movements.

[0247] Two interim analyses using Bayesian hierarchical modeling based on the binary
15 composite response were planned to evaluate:

1. Dose response and the allocation of patients to active treatment arms using a response adaptive randomization
2. Stopping accrual early with sufficient efficacy or futility

[0248] Interim analyses were conducted by a third-party biostatistician and firewalls were in
20 place to ensure interim results were not available to the sponsor or site investigators.

[0249] **Number of Patients (Planned and Analyzed):** It was planned to randomly assign 320 patients with IBS-D to treatment in the study. Randomization was stratified by history of cholecystectomy/gallbladder agenesis. A total of 1691 patients were screened and 320 patients were randomly assigned to 1 of the 3 treatment groups (65 patients in the buprenorphine dimer
25 50 mg cohort, 127 patients in the buprenorphine dimer 100 mg cohort, and 128 patients in the placebo cohort).

[0250] **Diagnosis and Main Criteria for Inclusion and Exclusion:**

[0251] Inclusion Criteria: Male and female patients of 18 to 75 years of age, inclusive, with a diagnosis of IBS-D based on the Rome IV Diagnostic Criteria. To be eligible for randomization

into the double-blind treatment phase, patients were required to meet all 4 of the following conditions:

1. Completed the daily eDiary for at least 6 of 7 days during the week before randomization and for at least 11 of 14 days during the 2 weeks before randomization;
 - 5 2. Had a weekly average of worst abdominal pain scores in the past 24 hours >3 on a 0-10 numeric rating scale for the week prior to randomization;
 3. Had an overall mean weekly stool consistency > 5 as assessed via Bristol Stool Form Score (BSFS) for the week prior to randomization; and
 4. Had not used loperamide within the 14 days prior to randomization.
- 10 **[0252]** Exclusion Criteria: Subjects who meet any of the following criteria during Screening will not be eligible to participate in the study:
1. History of clinically relevant pancreatic conditions including pancreatitis, pancreas divisum, or Sphincter of Oddi (SO) dysfunction with pancreatic manifestations;
 2. History of biliary pathology including acute cholecystitis within 6 months or biliary pain including post-cholecystectomy pain;
 - 15 3. Patients who have had biliary sphincterotomy with post-procedure persistent abnormal liver function transaminases (LFTs);
 4. Planned elective surgery within the next 4 months;
 5. Significant and/or severe medical illnesses such as cardiovascular, neurological,
 - 20 infectious, renal, hepatic or respiratory disorders that would interfere with the patient's medical care, participation in, or conduct of the study;
 6. History of intestinal obstruction, stricture, toxic megacolon, GI (gastro-intestinal) perforation, fecal impaction, gastric banding, bariatric surgery, adhesions, ischemic colitis, or impaired intestinal circulation (e.g. aorto-iliac disease);
 - 25 7. History of lactose intolerance uncontrolled on a lactose-free diet, or other malabsorption syndromes (e.g. fructose malabsorption);
 8. Dysphagia or difficulty swallowing pills;
 9. History of inflammatory bowel disease, celiac disease, Clostridium difficile colitis or have had recent unexplained GI bleeding within 3 months prior to screening;

10. History of major gastric, hepatic, pancreatic or intestinal surgery (appendectomy, hemorrhoidectomy, or polypectomy allowed as long as occurred > 3 months prior to trial screening; uncomplicated laparoscopic or open cholecystectomy is allowed if no history of post-operative biliary tract pain and surgery occurred > 3 months prior to screening);
5 and
11. Patients >40 years of age at high risk for colon cancer must have had a screening colonoscopy within the past 3 years prior to trial screening visit or > 50 years of age, must have had a normal screening colonoscopy within the past 10 years prior to trial screening visit. Patients with Lynch Syndrome or Familial Polyposis are excluded from
10 the study.

[0253] Test Product, Dose and Mode of Administration: Formula (I)

(dibuprenorphine-ethyl-ether) tablets, prepared as 25-mg or 100-mg immediate release tablets, administered as QD oral doses of 50 mg or 100 mg for a total of 12 weeks.

[0254] Control Product, Dose and Mode of Administration: Placebo matching

- 15 buprenorphine dimer tablets administered as QD oral doses for a total of 12 weeks.

[0255] Duration of Treatment: Study treatment was taken QD for 12 weeks. Each patient was enrolled in the study for approximately 19 weeks and study enrollment was expected to take approximately 16 to 20 months if all 320 patients were randomized. Therefore, the clinical portion of the study was expected to last up to approximately 25 months.

20 **[0256] Study Assessments:**

[0257] Efficacy assessments based on eDiary data included: daily entries for worst abdominal pain scores; abdominal discomfort scores; abdominal bloating scores; BSFS; bowel movement frequency, urgency, and incontinence; IBS-D Global Symptom Score; weekly entries for IBS-abdominal relief (IBS-AR); monthly entries for IBS-QoL and IBS-Inflammatory Bowel

- 25 Syndrome-Severity Scoring System (IBS-SSS); and completion of Patient Global Impression of Change (PGIC) at Week 12.

[0258] Safety evaluations included the monitoring of AEs, clinical laboratory assessments, 12-lead electrocardiograms (ECGs), vital signs measurements, physical examination findings

(including neurological exam), concomitant medications, and pregnancy tests for women of childbearing potential.

[0259] Patients who experienced an uncharacteristic clinically relevant change in the location, severity, and/or quality of their typical IBS abdominal pain, or colicky right upper quadrant and/or epigastric pain (either with or without associated, nausea, vomiting, anorexia, or radiation into back), or who experienced an exacerbation of abdominal pain that prompted withdrawal from the study should have immediately had blood drawn for lipase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, alkaline phosphatase (ALK-P), and buprenorphine dimer plasma concentration. Patients who experienced severe constipation, persisting potential abuse-related AEs, or a serious AE (SAE) should, as soon as possible, have had a blood draw for the determination of buprenorphine dimer plasma concentration.

[0260] There was a single blood draw per patient on Day 14 between 4 and 6 hours post-dose for measurement of plasma concentrations of buprenorphine dimer and its metabolites.

15 [0261] **Endpoints:**

[0262] Primary Efficacy Endpoint: The primary endpoint was the study composite responder status determined over the 12-week treatment period. A patient was defined as a study composite responder if he or she met the daily composite response criteria for at least 50% of days with eDiary entry during the interval of Days 1-84. To be eligible to be a responder, a patient must have had a minimum of 60 days of eDiary entries over the interval of Days 1-84. Any patient with fewer than 60 days of eDiary entries was considered a non-responder.

[0263] A patient must have met BOTH of the following criteria on a given day for a daily response:

- Pain response: worst abdominal pain score in the past 24 hours improved $\geq 30\%$ compared to the average in the week prior to randomization
- Stool consistency response: the average BSFS score of all reported bowel movements on the specific day (daily average) must be < 6 or the absence of a bowel movement if accompanied by $\geq 30\%$ improvement in worst abdominal pain

[0264] Secondary Efficacy Endpoints: The following secondary efficacy endpoints were analyzed: further analysis of the composite endpoint, modified composite, pain, stool consistency, IBS global symptom ratings, IBS-AR, and other IBS symptoms (bloating, discomfort, frequency, and incontinence).

- 5 [0265] Exploratory Endpoints: Quality of life assessments, PGIC, and urgency were analyzed as exploratory endpoints.

[0266] Safety Variables: Safety variables included adverse events (AEs, including SAEs and AEs of special interest), vital signs, weight, ECGs, physical examinations, hematology, and serum chemistry.

- 10 [0267] **Statistical Methods**: At the final analysis, which occurred approximately 12 weeks after the last patient was randomized, a one-sided p-value was calculated for the two-sample proportion test comparing all patients in the optimal active arm versus placebo. The active dose was considered superior to placebo if the corresponding one-sided p-value is ≤ 0.030 . This threshold was chosen to control the overall one-sided Type 1 error (with multiple interim
15 analyses and multiple doses) at approximately 0.05.

[0268] The secondary efficacy endpoint analyses were as follows:

- Treatment effect was assessed via pairwise, one-sided Cochran-Mantel-Haenszel (CMH) tests for each active treatment versus placebo, stratified by history of cholecystectomy/gallbladder agenesis.
- 20 • Treatment effect was assessed via pairwise, one-sided CMH tests for all patients on active treatments pooled versus placebo, stratified by history of cholecystectomy/gallbladder agenesis.
- Pain responders over the interval from Weeks 1-12: defined as those patients who met the daily pain response criteria for at least 50% of days with eDiary entry during the interval.
25 To be eligible to be a responder, a patient must have had a minimum of 60 days of eDiary entries over the 12-week interval.
- Stool consistency responders over the interval from Weeks 1-12: defined as those patients who met the daily stool consistency response criteria for at least 50% of days with eDiary

entry during the interval. To be eligible to be a responder, a patient must have had a minimum of 60 days of eDiary entries over the 12-week interval.

- IBS Global Symptom Score: Change from baseline for interval from Weeks 1-12.
A responder was defined as IBS global symptom score of 0 (none) or 1 (mild) or daily IBS symptom score improved by ≥ 2.0 compared to the average in the week prior to randomization. A minimum of 60 days of eDiary entries over the 12-week interval was required for responders.
- IBS-Abdominal Relief (IBS-AR): Percent responder over the interval from Weeks 1-12, defined as those patients with a weekly response of “Yes” to adequate relief of their IBS symptoms for at least 50% of the total weeks during the interval.
- As a secondary endpoint, a modified composite responder endpoint was analyzed, in which a daily responder was defined as:
 - Pain response: worst abdominal pain score in the past 24 hours improved $\geq 30\%$ compared to the average in the week prior to randomization
 - Stool consistency response: the BSFS for all reported bowel movements on the specific day must have been < 6 or the absence of a bowel movement if accompanied by $\geq 30\%$ improvement in worst abdominal pain
- Other IBS symptoms:
 - Discomfort: Change from baseline in daily abdominal discomfort scores
 - Bloating: Change from baseline in daily abdominal bloating scores
 - Frequency: Change from baseline in mean number of bowel movements per day
 - Incontinence: Change from baseline in mean number of bowel incontinence episodes per day as well as the number of incontinence-free days

[0269] Exploratory endpoints were as follows:

- IBS-Quality of Life (IBS-QOL) Responder: defined as a patient who achieved at least a 14-point improvement in IBS-QoL total score, evaluated at applicable visit compared to baseline IBS-QoL total score.
- IBS-Severity Scoring System (IBS-SSS) Responder: defined as a patient who had a ≥ 50 -point reduction in IBS-SSS total score, evaluated at applicable visit compared to baseline IBS-SSS total score.

- Patient Global Impression of Change (PGIC) Score: At Week 12, patients were asked to complete the PGIC assessment to rate their symptoms of IBS-D status compared with the beginning of the study.
 - Diary-defined constipation: Defined as an average BSFS score of <2 over any study week based on the electronic diary entries.
 - Other exploratory IBS Symptoms: The following diary endpoint was measured daily in the electronic diary:
 - Urgency (number of urgency episodes)
 - Urgency-free days
- 10 [0270] The composite endpoint, abdominal pain, and stool consistency at Week 12 were analyzed within each category of the following subgroup variables:
- Baseline C4 status (normal or elevated)
 - Baseline CRP status (normal or elevated)
 - PPI use (yes, no)
- 15 [0271] Safety variables were summarized using descriptive statistics. Summaries of treatment-emergent AEs (TEAEs), AEs leading to withdrawal, and SAEs, as well as a summary of AEs of special interest (AESIs), including severe constipation, new onset abdominal pain (with or without associated nausea, vomiting, anorexia, or radiation to the back), and potential abuse-related AEs, were assessed. Answers to questions in the QoL instruments were not
- 20 considered as AEs; however, for a sensitivity analysis, certain answers were assumed to be “QoL Potential AEs” and summarized separately.
- [0272] Plasma concentration data were listed.

Example 10: A Double Blind, Placebo Controlled, Phase 2 Study – Results

- [0273] Patient disposition: A total of 1691 patients were assessed for eligibility and
- 25 320 patients were randomly assigned to 1 of 3 treatment groups. The percentage of patients who completed active treatment was 78.5% in the buprenorphine dimer 50 mg treatment group and 83.5% in the buprenorphine dimer 100 mg treatment group. The most common reasons for

discontinuing active treatment were adverse events, loss of patient to follow-up, and withdrawal by patient.

5 [0274] Demography and Baseline Characteristics: The mean age of all patients was 43.6 years (range: 19 years to 75 years). The majority of patients reported race as white (256 [80.0%]) and ethnicity as Not Hispanic or Latino (290 [90.6%]). The youngest cohort was buprenorphine dimer 100 mg with a mean age of 42.3 years. The oldest group was buprenorphine dimer 50 mg with a mean age of 44.8 years. Overall, 70.3% of patients were female. The mean body mass index (BMI) was 33.1 kg/m² (range 17-65). The lowest BMI group was buprenorphine dimer 50 mg with a mean BMI of 32.1 and the highest BMI group was buprenorphine dimer 100 mg with
10 a mean BMI of 34.2.

[0275] Eighty-five (85) patients who had a previous cholecystectomy were enrolled in the study, 27% of the total randomized patients.

[0276] Baseline levels of CRP were within normal range in 229 patients and elevated in 87. Baseline levels of C4 were normal in 254 patients and elevated in 58. Sixty-three (63) patients
15 used proton pump inhibitors and 257 did not. Baseline CRP and C4 levels were not available for some patients.

Primary Efficacy Endpoint Results:

[0277] For the primary endpoint (composite response), in the intent-to-treat (ITT) analysis set (n=320), responder proportions for buprenorphine dimer 50 mg, 100 mg, and placebo cohorts
20 were 16.9%, 28.3%, and 21.9%, respectively (100 mg vs. placebo p=0.117).

[0278] To account for potential study effect of COVID-19, the statistical analysis plan (SAP) included two analysis sets, defined as “COVID-19 Affected” and “COVID-19 Per-Protocol Affected” (SAP Section 4.3.4 and Section 4.3.5). “COVID-19 Affected” patients were defined as those with a recorded adverse event of “COVID-19” (n=11). “COVID-19 Per-Protocol
25 Affected” patients were those who had an assessment of COVID-19 or a protocol deviation related to COVID-19 (n=20). Composite responder proportions among the ITT analysis set excluding COVID-19 Per-Protocol Affected Patients (n=300) for buprenorphine dimer 50 mg, 100 mg, and placebo cohorts were 18.3%, 29.5%, and 20.3%, respectively (100 mg vs. placebo p=0.051).

Primary Endpoint by Predefined Patient Subgroups

5 [0279] *Excessive Users of Loperamide (Rescue Medication)*: Given that excessive use of the rescue medication loperamide was notably more prevalent among patients in the placebo cohort, post-hoc analyses were conducted regarding those patients (n=37) as treatment failures (see description of Protocol-Compliant analysis set below).

10 [0280] *Protocol-Compliant Analysis Set*: Post-hoc analyses of the primary and key secondary and exploratory endpoints were conducted to determine outcomes for “Protocol-Compliant” patients, i.e., the ITT analysis set but excluding COVID-19 Per-Protocol Affected patients and regarding those with excessive loperamide use as treatment failures (referred to in this Study Report as the “Protocol-Compliant” analysis set, n=300). In this Protocol-Compliant analysis set, composite response proportions for the buprenorphine dimer 50 mg, 100 mg, and placebo cohorts were 16.7%, 27.0%, and 14.4%, respectively (100 mg vs. placebo p=0.008).

15 [0281] *Patients with Elevated vs. Normal C4 Levels*: Given low response rates among patients with elevated C4 levels compared to those with normal C4 levels, post-hoc analysis was conducted of the primary and other endpoints among patients in the Protocol-Compliant analysis set who had normal C4 levels at baseline (n=240) in order to determine the best patient population for future investigation. Composite responder proportions among the Protocol-Compliant analysis set with normal C4 levels in the buprenorphine dimer 50 mg, 100 mg, and placebo cohorts were 19.6%, 31.6%, and 15.4%, respectively (100 mg vs. placebo p=0.005) (FIG. 13). No patient in the Protocol-Compliant analysis set with elevated C4 levels was a composite responder, in any of the three cohorts.

25 [0282] *Post-Cholecystectomy Patients*: A similar post-hoc analysis was conducted on the Protocol-Compliant analysis set among only those patients without gallbladders (post-cholecystectomy patients, n=85). Composite responder proportions among Protocol-Compliant post-cholecystectomy patients for buprenorphine dimer 50 mg, 100 mg, and placebo cohorts were 13.3%, 28.6%, and 11.4%, respectively (100 mg vs. placebo p=0.036).

[0283] FIG. 14 shows composite responder proportions by treatment, week 1-12, among post-cholecystectomy patient with normal C4 levels at baseline. ITT analysis set excluding COVID-19 per-Protocol affected patients and treating excessive loperamide users as non-responders.

Secondary Efficacy Endpoint Results:

[0284] In the ITT analysis set, IBS-AR response rates of the buprenorphine dimer 100 mg cohort were statistically significantly better than those of placebo. buprenorphine dimer 50 mg and 100 mg response proportions were not significantly different from that of placebo for modified composite response, pain response, IBS-D global symptom ratings, or stool consistency.

[0285] In the Protocol-Compliant analysis set (post-hoc), buprenorphine dimer 100 mg response proportions were statistically significantly better than those of placebo for stool consistency and IBS-AR (p=0.022 and 0.007, respectively).

10 **Exploratory Endpoint Results:**

[0286] In the ITT analysis set, IBS-QOL response rates for the buprenorphine dimer 100 mg cohort were statistically significantly better than those of placebo. buprenorphine dimer 50 mg and 100 mg response proportions were not significantly different from that of placebo for other exploratory endpoints.

15 [0287] In the protocol-compliant analysis set (post-hoc), buprenorphine dimer 100 mg response proportions were statistically significantly better than those of placebo for IBS-QOL and IBS-SSS (p values vs. placebo were 0.020 and 0.044, respectively). The response rate of patients who indicated a PGIC score of “Much Improved” at Week 12 was significantly higher in the 100 mg cohort than placebo (p=0.038).

20 [0288] FIG. 15 shows therapeutic benefit across multiple endpoints in Protocol-compliant patients with normal C4 levels, treated with buprenorphine dimer. Buprenorphine dimer (which is a partial mu agonist and full kappa antagonist) effectively alleviates clinical distress in all IBS-D patients with and without gallbladder, whose abdominal pain is not caused by inflammation of the bowel, or the diarrhea is caused by malabsorption of bile acid.

25 Improvements in scores related Patients Global Impression of Change during and end of the trial, IBS-Adequate Relief, Symptom Severity, and Quality of Life demonstrate that patients feel and benefit from relief that follow treatment, and this relief extends beyond improvements in abdominal pain and diarrhea.

[0289] FIG. 16 shows therapeutic benefit across multiple endpoints in Protocol-compliant post-cholecystectomy patients with normal C4 levels, treated with buprenorphine dimer. The therapeutic benefits of buprenorphine dimer in IBS-D patients lacking gallbladder is more robust than patients with gallbladder.

- 5 [0290] FIG. 17 demonstrates that patients are more likely benefit from the buprenorphine dimer by adhering to the treatment protocol.

Safety Results:

- [0291] Eighteen (18) patients withdrew from the clinical trial due to AEs (4, 7, and 7 in the 50 mg, 100 mg, and placebo cohorts, respectively). Cumulatively, 4 patients (1 on 50 mg, 2 on 100 mg, and 2 on placebo) had serious TEAEs. None of these serious TEAEs were considered to be
10 related to study drug. No deaths were reported.

- [0292] A total of 14 AEs (3, 5, and 6 on the 50 mg, 100 mg, and placebo arms, respectively) of special interest (AESIs) were reported in 12 patients (3 [4.6%], 4 [3.2%], and 5 [3.9%] in the 50 mg, 100 mg, and placebo arms, respectively). Abdominal pain (including abdominal pain upper)
15 was the most frequently reported AESI in 0, 4 (3.2%), and 1 (0.8%) patients on the 50 mg, 100 mg, and placebo arms, respectively. All AESIs were non-serious.

Conclusions:

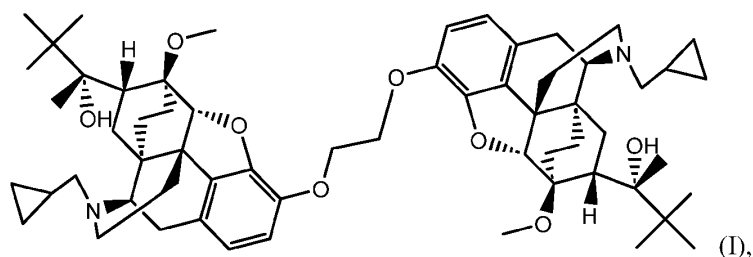
- [0293] Buprenorphine dimer 100 mg given once daily for 12 weeks was shown to be efficacious in patients with IBS-D who were compliant with the protocol and had normal C4
20 levels at the time of screening. This includes patients who had no gallbladder (were post-cholecystectomy). Buprenorphine dimer was safe and well tolerated, including in patients who were post-cholecystectomy. There were no clinical features suggestive of central nervous system effects.

- [0294] Although the foregoing invention has been described in some detail by way of
25 illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.

Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

- 1 1. A method of treating a disease in a human subject in need thereof,
2 comprising orally administering to the subject a therapeutically effective amount of a
3 buprenorphine dimer represented by formula (I):



- 5 or a pharmaceutically acceptable salt thereof, wherein
6 the therapeutically effective amount of the buprenorphine dimer is a total daily
7 dose of at least about 100 mg per day on a salt-free and anhydrous basis; and
8 the administering achieves a plasma concentration of at least about 700 ng/mL in
9 the subject.

- 1 2. The method of claim 1, wherein the buprenorphine dimer is in a neutral
2 form, represented by formula (I).

- 1 3. The method of claim 1 or 2, wherein the therapeutically effective amount
2 of the buprenorphine dimer is a total daily dose of at least about 200 mg per day on a salt-free
3 and anhydrous basis.

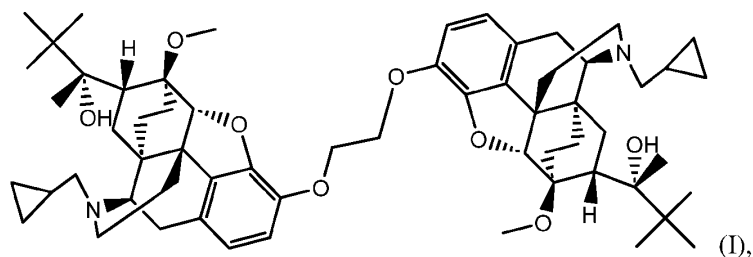
- 1 4. The method any one of claims 1-3, wherein the buprenorphine dimer is
2 administered once daily.

- 1 5. The method of any one of claims 1-3, wherein the buprenorphine dimer is
2 administered twice daily.

- 1 6. The method of any one of claims 1-5, wherein the disease is chronic pain.

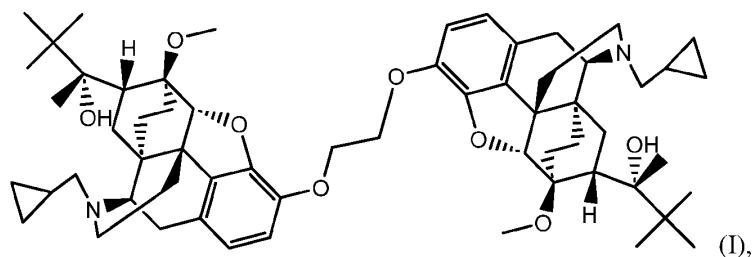
- 1 7. The method of any one of claims 1-5, wherein the disease is Irritable
2 Bowel Syndrome with Diarrhea (IBS-D).

3 **8.** A method of treating a chronic pain in a subject in need thereof,
4 comprising administering to the subject a therapeutically effective amount of a buprenorphine
5 dimer represented by formula (I):



6 or a pharmaceutically acceptable salt thereof, wherein the buprenorphine dimer is administered
8 orally.

1 **9.** A method of treating a chronic pain in a subject in need thereof,
2 comprising administering to the subject a pharmaceutical composition comprising a
3 therapeutically effective amount of a buprenorphine dimer in a neutral form represented by
4 formula (I):



6 wherein the pharmaceutical composition is administered orally.

1 **10.** The method of claim 8 or 9, wherein the chronic pain is a nociceptive
2 pain, a neuropathic pain, or a combination thereof.

1 **11.** The method of any one of claims 8 to 10, wherein the chronic pain is a
2 peripheral chronic pain.

1 **12.** The method of any one of claims 8 to 11, wherein the chronic pain is
2 peripheral neuropathic pain.

1 **13.** The method of any one of claims **8** to **12**, wherein the subject has a sickle
2 cell disease (SCD), cancer and/or under chemotherapy, HIV, diabetes, shingles, a traumatic
3 injury, a surgery, an amputation, a burn, or a combination thereof; and/or the subject has or had a
4 coronavirus disease.

1 **14.** The method of any one of claims **8** to **13**, wherein the chronic pain is any
2 one of 1) to 10):
3 1) associated with a sickle cell disease (SCD) in the subject;
4 2) a chemotherapeutic induced neuropathic pain in the subject who has cancer and under
5 chemotherapy;
6 3) HIV sensory neuropathy;
7 4) a diabetic neuropathy pain;
8 5) a post-herpetic neuralgia in the subject who has or had shingles;
9 6) a post-trauma chronic pain;
10 7) a post-surgical pain;
11 8) a post-amputation pain;
12 9) a post-burn pain; and
13 10) associated with a long-term effect in the subject who had a coronavirus disease.

1 **15.** The method of any one of claims **8** to **14**, wherein the therapeutically
2 effective amount is a total daily dosage of from about 50 mg to about 800 mg, from about 50 mg
3 to about 700 mg, from about 50 mg to about 600 mg, from about 50 mg to about 500 mg, from
4 about 50 mg to about 400 mg, from about 50 mg to about 300 mg, or from about 50 mg to about
5 250 mg of the buprenorphine dimer on a salt-free and anhydrous basis.

1 **16.** The method of claim **15**, wherein the therapeutically effective amount is a
2 total daily dosage of about 100 mg of the buprenorphine dimer on a salt-free and anhydrous
3 basis.

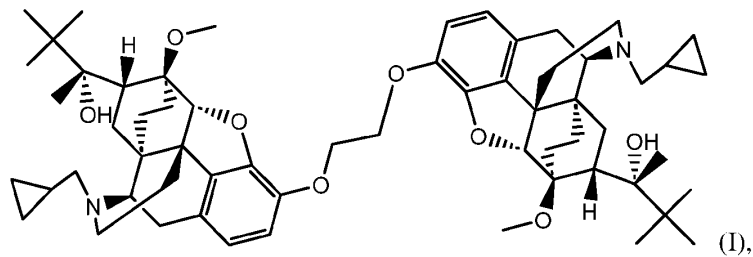
1 **17.** The method of claim **15**, wherein the therapeutically effective amount is a
2 total daily dosage of about 200 mg of the buprenorphine dimer on a salt-free and anhydrous
3 basis.

- 1 **18.** The method of any one of claims **8** to **17**, wherein the buprenorphine
2 dimer is administered once, twice, three times, or four times daily.
- 1 **19.** The method of claim **18**, wherein the buprenorphine dimer is administered
2 once daily.
- 1 **20.** The method of claim **18**, wherein the buprenorphine dimer is administered
2 twice daily.
- 1 **21.** The method of any one of claims **9** to **20**, wherein the pharmaceutical
2 composition comprising the buprenorphine dimer is a tablet.
- 1 **22.** The method of claim **21**, wherein the tablet comprising buprenorphine
2 dimer is an immediate-release tablet.
- 1 **23.** The method of any one of claims **8** to **22**, wherein the therapeutically
2 effective amount of the buprenorphine dimer reduces the chronic pain, measured by one or more
3 criteria selected from the group consisting of:
4 1) a reduced monthly average score on a 0-10 Likert scale over past 1, 3, or 6 months,
5 relative to a monthly average score prior to the treating;
6 2) a reduced monthly average score of characteristic pain intensity and/or disability over past
7 1, 3, or 6 months, relative to a monthly average score prior to the treating; and
8 3) a reduced pain severity over past 1, 3, or 6 months relative to a pain severity prior to the
9 treating, wherein the reduced pain severity is selected from the group consisting of:
10 i) from Grade 4 (high disability-severely limiting) to any one of Grade 3 (high disability-
11 moderately limiting), Grade 2 (low disability-high intensity), Grade 1 (low
12 disability-low intensity), and Grade 0 (no pain);
13 ii) from Grade 3 to any one of Grade 2, Grade 1, and Grade 0;
14 iii) from Grade 2 to Grade 1 or Grade 0; and
15 iv) from Grade 1 to Grade 0.
- 1 **24.** The method of any one of claims **8** to **23**, wherein the therapeutically
2 effective amount of the buprenorphine dimer provides an antihyperalgesic effect.

1 **25.** The method of any one of claims **8** to **24**, wherein, during or after the
2 treating, the subject has reduced hyperalgesia or is substantially free of hyperalgesia.

1 **26.** The method of claim **25**, wherein, during or after the treating, the subject
2 is free of hyperalgesia.

1 **27.** A method of treating Irritable Bowel Syndrome with Diarrhea (IBS-D) in
2 a subject in need thereof, comprising administering to the subject a therapeutically effective
3 amount of a buprenorphine dimer represented by formula (I):



5 or a pharmaceutically acceptable salt thereof, wherein the subject has 7 α -hydroxy-4-cholesten-3-
6 one (C4) at a level of no more than 50 milligrams per deciliter (mg/dL) in blood.

1 **28.** The method of claim 27, wherein

2 (a) the subject has a C4 level of from about 15 mg/dL to about 45 mg/dL in blood; and/or

(b) prior to the treating, the subject has worst abdominal pain over past 24 hours in a weekly average score of more than 3, based on a 1-10 numeric rating scale; and/or

(c) prior to the treating, the subject has stool consistency in a weekly average score of greater than 5, as assessed via Bristol Stool Form Score (BSFS); and/or

7 (d) wherein the subject has cholecystectomy.

1 **29.** The method of claim **27** or **28**, wherein, during the treating, the subject
2 receives loperamide.

1 **30.** The method of any one of claims **27** to **29**, wherein, during the treating,
 2 the subject receives loperamide in a total dosage of no more than any one of 8 mg over 24 hours,
 3 14 mg over 48 hours, and 22 mg over 7 days.

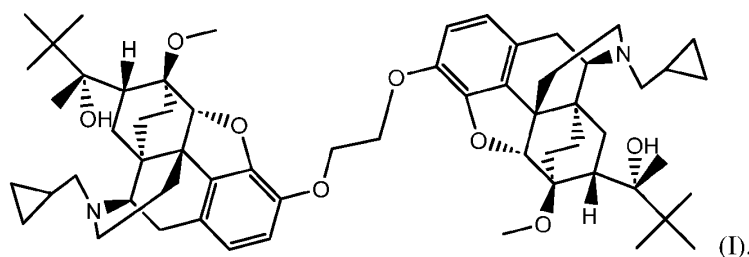
1 **31.** The method of any one of claims **29** or **28**, wherein, during the treating,
 2 the subject does not receive loperamide.

1 **32.** The method of any one of claims **29** to **30**, wherein the therapeutically
 2 effective amount of the buprenorphine dimer
 3 1) reduces a weekly average score of worst abdominal pain over past 24 hours by at least
 4 30%, relative to the weekly average score prior to the treating; and/or
 5 2) improves stool consistency, measured by i) a reduced average BSFS score to less than
 6 6, or ii) an absence of a bowel movement provided that features of 1) are met.

1 **33.** The method of any one of claims **8** to **32**, wherein the subject is human.

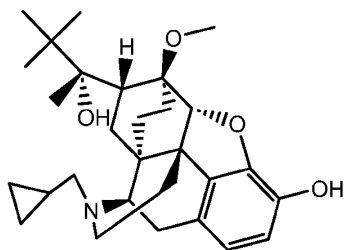
1 **34.** The method of claim **33**, wherein the human is an adult in an age of at
 2 least 18 years old.

1 **35.** A process for preparing a buprenorphine dimer in a neutral form,
 2 represented by formula (I):

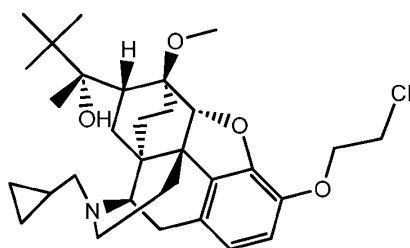


3
 4 comprising:

5 a) combining buprenorphine or a salt thereof, represented by the formula:



a first inorganic base, water, and a first phase-transfer agent in 1,2-dichloroethane to form a compound of formula (II):



(II); and

b) combining the compound of formula (II), buprenorphine or a salt thereof, a second inorganic base, water, and a second phase-transfer agent in an aprotic solvent to provide the buprenorphine dimer of formula (I) in a neutral form.

36. The process of claim **35**, wherein the buprenorphine in steps a) and b) are each a buprenorphine HCl salt.

37. The process of claim **35** or **36**, wherein the first and second inorganic bases are each an alkali hydroxide independently selected from the group consisting of LiOH, NaOH, KOH, and CsOH.

38. The process of claim **37**, wherein the first and second inorganic bases are each NaOH.

39. The process of any one of claims **35** to **38**, wherein the first and second phase-transfer agents are each independently a quaternary ammonium salt.

40. The process of claim **39**, wherein the first and second phase-transfer agents are each tetrabutylammonium hydroxide.

1 **41.** The process of claim **40**, wherein, in step a), tetrabutylammonium
2 hydroxide is present in an amount of about 5% by weight, based on buprenorphine or the salt
3 thereof; and/or in step b), tetrabutylammonium hydroxide is present in an amount of about 0.3
4 equivalents, relative to the compound of formula (II).

1 **42.** The process of any one of claims **35** to **41**, wherein, in step b),
2 buprenorphine or the salt thereof is present in an amount of about 0.8 equivalents, relative to the
3 compound of formula (II).

1 **43.** The process of any one of claims **35** to **42**, wherein, in step b), the aprotic
2 solvent is toluene.

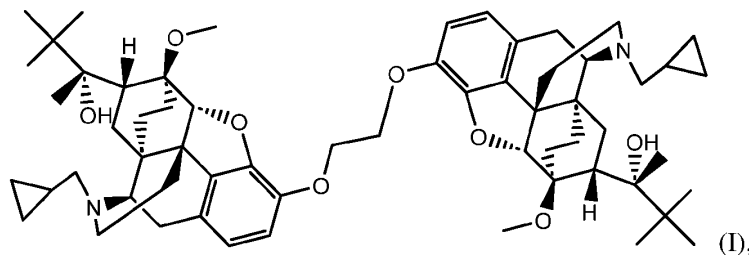
1 **44.** The process of any one of claims **35** to **43**, wherein step a) is conducted at
2 a temperature of from about 50°C to about 70°C; and/or step b) is conducted at a temperature of
3 from about 70°C to about 100°C.

1 **45.** The process of claim **44**, wherein step a) is conducted at a temperature of
2 about 60°C; and/or step b) is conducted at a temperature of from about 85°C.

1 **46.** The process of any one of claims **35** to **45**, wherein the compound of
2 formula (II) obtained from step a) is used directly in step b) without purification.

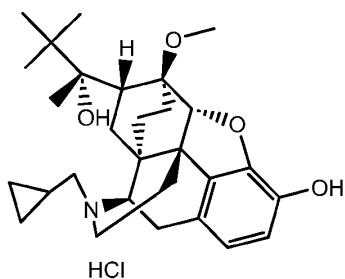
1 **47.** The process of any one of claims **35** to **46**, wherein the buprenorphine
2 dimer of formula (I) in a neutral form is further purified by trituration in acetone.

1 **48.** A process for preparing a buprenorphine dimer in a neutral form,
2 represented by formula (I):

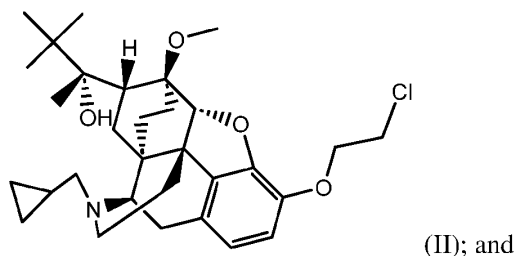


3
4 comprising:

5 a) combining a HCl salt of buprenorphine, represented by the formula:



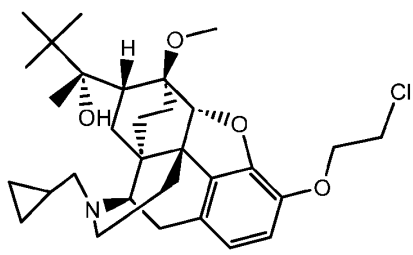
6
7 an aqueous NaOH solution, and tetrabutylammonium hydroxide in 1,2-dichloroethane to
8 form a compound of formula (II):



10 b) combining the compound of formula (II), a HCl salt of buprenorphine, an
11 aqueous NaOH solution, and tetrabutylammonium hydroxide in toluene to provide the
12 buprenorphine dimer of formula (I) in a neutral form.

1

1 **49.** A compound, represented by formula (II):



2

3 or a salt thereof.

50. The compound of claim **49**, in a neutral form.