TOPICAL FORMULATIONS OF CALCIUM CHANNEL BLOCKERS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/610,218, filed December 14, 2023, which is hereby incorporated by reference in its entirety for all purposes.

BACKGROUND

[0002] Chronic pain has been called the U.S.'s leading public health problem by the American Pain Society with up to 50 million Americans suffering from chronic pain. Neuropathic pain is one of the most challenging neurological diseases to treat and, neuropathic pain often becomes a chronic condition. Current therapies for neuropathic pain such as antiepileptics (*e.g.*, gabapentin and pregabalin) and antidepressants (*e.g.*, amitriptyline and duloxetine) do not address the underlying causes of pain and, therefore, show efficacy in only a fraction of patients.

[0003] Orally administered 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one has been considered for the treatment of neuropathic pain; however, a potential narrow therapeutic index from oral administration may hinder its human application.

[0004] Thus, there is a need for formulations of 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one that provide the compound's therapeutic benefit by providing high exposure directly on the target under the skin without high systemic exposure.

SUMMARY OF THE DISCLOSURE

[0005] Aspects of the present disclosure provide a pharmaceutical composition for the topical treatment of pain comprising:

about 0.1% to about 10% by weight of 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("Compound 1") or 3-(2-(4-((4-fluorophenyl)(hydroxy)methyl)piperidin-1-yl)ethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("Compound 2") or a pharmaceutically acceptable salt thereof,

wherein the topical administration of an effective amount of the composition to a patient in need thereof provides a maximum plasma concentration (C_{max}) of Compound 1 or Compound 2 of less than about 25 ng/mL.

[0006] In one aspect, the present disclosure provides a pharmaceutical composition for the topical treatment of pain comprising:

about 0.1% to about 10% by weight of Compound 1 or Compound 2, or a pharmaceutically acceptable salt thereof,

about 20% to about 60% (wt/wt%) of a permeation enhancer;

about 35% to about 55% (wt/wt%) of a solvent; and

about 1% to about 10% (wt/wt%) of a gelling agent.

DETAILED DESCRIPTION

[0007] The present disclosure relates to topical pharmaceutical compositions comprising 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("Compound 1") or (3-(2-(4-((4-fluorophenyl)(hydroxy)methyl)piperidin-1-yl)ethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one) ("Compound 2"), or pharmaceutically acceptable salts thereof that are useful for the topical treatment or management of pain. The topical pharmaceutical compositions described herein provide minimal systemic (plasma) drug levels (therefore typical side effects of systemic administration may be reduced, minimized or eliminated) while maintaining *in vivo* pharmacological effects necessary for the effective treatment or management of pain. The compositions can be administered at an efficacious dose without high systemic exposure of Compound 1 or Compound 2.

Definitions

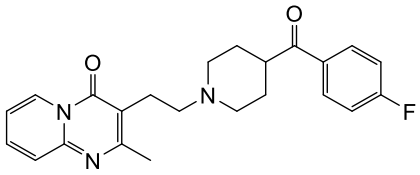
[0008] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0009] The term "about" when immediately preceding a numerical value means a range (e.g., plus or minus 10% of that value). For example, "about 50" can mean 45 to 55, "about 25,000" can mean 22,500 to 27,500, etc., unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation. For example, in a list of numerical values such as "about

49, about 50, about 55, ... ", "about 50" means a range extending to less than half the interval(s) between the preceding and subsequent values, e.g., more than 49.5 to less than 50.5. Furthermore, the phrases "less than about" a value or "greater than about" a value should be understood in view of the definition of the term "about" provided herein. Similarly, the term "about" when preceding a series of numerical values or a range of values (e.g., "about 10, 20, 30" or "about 10-30") refers, respectively to all values in the series, or the endpoints of the range.

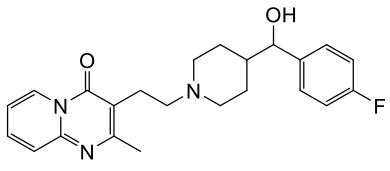
[0010] The terms "administer," "administering" or "administration" as used herein refer to administering a compound or pharmaceutically acceptable salt of the compound or a composition comprising the compound or pharmaceutically acceptable salt of the compound to a patient.

[0011] The term “Compound 1” as used herein corresponds to 3-{2-[4-(4-fluorobenzoyl)piperidin-1-yl]ethyl}-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. “Compound 1” has the following structural formula:



(“Compound 1”).

[0012] The term “Compound 2” as used herein corresponds to 3-(2-(4-((4-fluorophenyl)(hydroxy)methyl)piperidin-1-yl)ethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. “Compound 2” has the structure shown below:



(“Compound 2”);

[0013] The term “treating” as used herein with regard to a patient or subject, refers to improving at least one symptom of the patient's or subject’s disorder. In embodiments, treating can be improving, or at least partially ameliorating a disorder or one or more symptoms of a disorder.

[0014] The terms "effective amount" and "therapeutically effective amount" are used interchangeably in this disclosure and refer to an amount of a compound, or a salt thereof, (or pharmaceutical composition containing the compound or salt) that, when administered to a patient, is capable of performing the intended result. The "effective amount" will vary depending on the

active ingredient, the state, disorder, or condition to be treated and its severity, and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0015] The term "pharmaceutically acceptable salt" includes both acid and base addition salts. Pharmaceutically acceptable salts include those obtained by reacting the active compound functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, acetate, tartrate, oleate, fumarate, formate, benzoate, glutamate, methanesulfonate, benzenesulfonate, and p-toluenesulfonate salts. Base addition salts include but are not limited to, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris-(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine, dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, *e.g.*, lysine and arginine dicyclohexylamine and the like. Examples of metal salts include lithium, sodium, potassium, magnesium, calcium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.

[0016] The term "pharmaceutically acceptable carrier" as used herein includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. A "pharmaceutically acceptable carrier," after administered to or upon a subject, does not cause undesirable physiological effects. The carrier in the pharmaceutical composition must be "acceptable" also in the sense that it is compatible with the active ingredient and can be capable of stabilizing it. One or more solubilizing agents can be utilized as pharmaceutical carriers for delivery of an active agent. Examples of a

pharmaceutically acceptable carrier include, but are not limited to, permeation enhancers, emulsifiers, thickeners, emollients, biocompatible vehicles, adjuvants, additives, and diluents to achieve a composition usable as a dosage form. Examples of other carriers include colloidal silicon oxide, magnesium stearate, cellulose, and sodium lauryl sulfate. Additional suitable pharmaceutical carriers and diluents, as well as pharmaceutical necessities for their use, are described in Remington's Pharmaceutical Sciences. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal, topical, or epidermal administration (e.g., by injection or infusion). The therapeutic compounds may include one or more pharmaceutically acceptable salts.

Compositions

[0017] In one aspect, the present disclosure provides pharmaceutical compositions comprising Compound 1 or Compound 2, or a pharmaceutically salt thereof that are useful for the topical treatment of pain.

[0018] In embodiments, the present disclosure provides pharmaceutical compositions for the topical treatment of pain comprising Compound 1 or a pharmaceutically acceptable salt thereof, wherein the topical administration of an effective amount of the composition to a patient in need thereof provides a maximum plasma concentration (C_{max}) of Compound 1 of less than about 25 ng/mL. In embodiments, the topical administration of an effective amount of the composition to a patient in need thereof provides a C_{max} of Compound 1 of about 0.1 ng/mL to about 100 ng/mL, about 0.2 ng/mL to about 100 ng/mL, about 0.5 ng/mL to about 100 ng/mL, about 1 ng/mL to about 100 ng/mL, about 0.1 ng/mL to about 50 ng/mL, about 0.2 ng/mL to about 50 ng/mL, about 0.5 ng/mL to about 50 ng/mL, about 1 ng/mL to about 50 ng/mL, about 0.1 ng/mL to about 35 ng/mL, about 0.2 ng/mL to about 35 ng/mL, about 0.5 ng/mL to about 35 ng/mL, about 1 ng/mL to about 35 ng/mL, about 0.1 ng/mL to about 25 ng/mL, about 0.2 ng/mL to about 25 ng/mL, about 0.5 ng/mL to about 25 ng/mL, about 1 ng/mL to about 25 ng/mL, about 0.1 ng/mL to about 20 ng/mL, about 0.2 ng/mL to about 20 ng/mL, about 0.5 ng/mL to about 20 ng/mL, about 1 ng/mL to about 20 ng/mL, about 0.1 ng/mL to about 10 ng/mL, about 0.2 ng/mL to about 10 ng/mL, about 0.5 ng/mL to about 10 ng/mL, about 1 ng/mL to about 10 ng/mL, about 0.1 ng/mL to about 5 ng/mL, 0.2 ng/mL to about 5 ng/mL, about 0.5 ng/mL to about 5 ng/mL, about 1 ng/mL to about 5 ng/mL, less than about 50 ng/mL, less than 25 ng/mL, less than about 10 ng/mL, less than about 5 ng/mL, or less than about 1 ng/mL, for example, about less than about 50 ng/mL, less than about 48 ng/mL, less than about 46 ng/mL, less than about 44 ng/mL, less than about 42

ng/mL, less than about 40 ng/mL, less than about 38 ng/mL, less than about 36 ng/mL, less than about 34 ng/mL, less than about 32 ng/mL, less than about 30 ng/mL, less than about 28 ng/mL, less than about 26 ng/mL, less than about 24 ng/mL, less than about 22 ng/mL, less than about 20 ng/mL, less than about 18 ng/mL, less than about 16 ng/mL, less than about 14 ng/mL, less than about 12 ng/mL, less than about 10 ng/mL, less than about 8 ng/mL, less than about 6 ng/mL, less than about 4 ng/mL, less than about 2 ng/mL, less than about 1.5 ng/mL, less than about 1.3 ng/mL, less than about 1 ng/mL, less than about 0.8 ng/mL, less than about 0.5 ng/mL, about 25 ng/mL, about 22 ng/mL, about 20 ng/mL, about 18 ng/mL, about 16 ng/mL, about 14 ng/mL, about 12 ng/mL, about 10 ng/mL, about 8 ng/mL, about 6 ng/mL, about 4 ng/mL, about 2 ng/mL, about 1.5 ng/mL, about 1.3 ng/mL, about 1 ng/mL, about 0.5 ng/mL, or about 0.2 ng/mL, including any values or ranges therebetween. In embodiments the topical administration of an effective amount of the composition to a patient in need thereof provides a C_{max} of Compound 1 of less than about 25 ng/mL, less than about 22 ng/mL, less than about 20 ng/mL, less than about 18 ng/mL, less than about 16 ng/mL, less than about 14 ng/mL, less than about 12 ng/mL, less than about 10 ng/mL, less than about 5 ng/mL, less than about 2 ng/mL, or less than about 1 ng/mL, including any values or ranges therebetween. In embodiments, the maximum plasma concentration (C_{max}) of Compound 1 following topical administration of the composition is lower than the limit of quantification, determined by conventionally using analytical methods in the art (*e.g.,* liquid chromatography-mass spectrometry, nuclear magnetic resonance spectroscopy, and gas chromatography-mass spectrometry). In embodiments, the maximum plasma concentration (C_{max}) of Compound 1 is less than 1.3 ng/mL.

[0019] In embodiments, the present disclosure provides pharmaceutical compositions for the topical treatment of pain comprising Compound 2, or a pharmaceutically acceptable salt thereof, wherein the topical administration of an effective amount of the composition to a patient in need thereof provides a C_{max} of Compound 2 of less than about 25 ng/mL. In embodiments, the topical administration of an effective amount of the composition to a patient in need thereof provides a C_{max} of Compound 2 of about 0.1 ng/mL to about 100 ng/mL, 0.2ng/mL to about 100 ng/mL, about 0.5 ng/mL to about 100 ng/mL, about 1 ng/mL to about 100 ng/mL, about 0.1 ng/mL to about 50 ng/mL, about 0.2 ng/mL to about 50 ng/mL, about 0.5 ng/mL to about 50 ng/mL, about 1 ng/mL to about 50 ng/mL, about 0.1 ng/mL to about 35 ng/mL, about 0.2 ng/mL to about 35 ng/mL, about 0.5 ng/mL to about 35 ng/mL, about 1 ng/mL to about 35 ng/mL, about 0.1 ng/mL to about 25 ng/mL, about 0.2 ng/mL to about 25 ng/mL, about 0.5 ng/mL to about 25 ng/mL, about 1 ng/mL to about 25 ng/mL, about 0.1 ng/mL to about 20 ng/mL, about 0.2 ng/mL

to about 20 ng/mL, about 0.5 ng/mL to about 20 ng/mL, about 1 ng/mL to about 20 ng/mL, about 0.1 ng/mL to about 10 ng/mL, about 0.2 ng/mL to about 10 ng/mL, about 0.5 ng/mL to about 10 ng/mL, about 1 ng/mL to about 10 ng/mL, about 0.1 ng/mL to about 5 ng/mL, 0.2 ng/mL to about 5 ng/mL, about 0.5 ng/mL to about 5 ng/mL, about 1 ng/mL to about 5 ng/mL, less than about 100 ng/mL, less than about 50 ng/mL, less than 25 ng/mL, less than about 10 ng/mL, less than about 5 ng/mL, or less than about 1 ng/mL, for example, about less than about 50 ng/mL, less than about 48 ng/mL, less than about 46 ng/mL, less than about 44 ng/mL, less than about 42 ng/mL, less than about 40 ng/mL, less than about 38 ng/mL, less than about 36 ng/mL, less than about 34 ng/mL, less than about 32 ng/mL, less than about 30 ng/mL, less than about 28 ng/mL, less than about 26 ng/mL, less than about 24 ng/mL, less than about 22 ng/mL, less than about 20 ng/mL, less than about 18 ng/mL, less than about 16 ng/mL, less than about 14 ng/mL, less than about 12 ng/mL, less than about 10 ng/mL, less than about 8 ng/mL, less than about 6 ng/mL, less than about 4 ng/mL, less than about 2 ng/mL, less than about 1.5 ng/mL, less than about 1.3 ng/mL, less than about 1 ng/mL, less than about 0.8 ng/mL, less than about 0.5 ng/mL, about 25 ng/mL, about 22 ng/mL, about 20 ng/mL, about 18 ng/mL, about 16 ng/mL, about 14 ng/mL, about 12 ng/mL, about 10 ng/mL, about 8 ng/mL, about 6 ng/mL, about 4 ng/mL, about 2 ng/mL, about 1.5 ng/mL, about 1.3 ng/mL, about 1 ng/mL, about 0.5 ng/mL, or about 0.2 ng/mL, including any values or ranges therebetween. In embodiments, the topical administration of an effective amount of the composition to a patient in need thereof provides a C_{max} of Compound 2 of less than about 25 ng/mL, less than about 22 ng/mL, less than about 20 ng/mL, less than about 18 ng/mL, less than about 16 ng/mL, less than about 14 ng/mL, less than about 12 ng/mL, less than about 10 ng/mL, less than about 5 ng/mL, less than about 2 ng/mL, or less than about 1 ng/mL, including any values or ranges therebetween. In embodiments, the maximum plasma concentration (C_{max}) of Compound 2 is lower than the limit of quantification, determined by conventionally using analytical methods in the art (*e.g.,* liquid chromatography-mass spectrometry, nuclear magnetic resonance spectroscopy, and gas chromatography-mass spectrometry). In embodiments, the maximum plasma concentration (C_{max}) of Compound 1 is less than 1.3 ng/mL.

[0020] In embodiments, the present disclosure provides pharmaceutical compositions for the topical treatment of pain comprising about 0.02% to about 20%, by weight, Compound 1 or Compound 2, or a pharmaceutically salt thereof, *e.g.*, about 0.02%, about 0.04%, about 0.06%, about 0.08%, about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, about 5%, about 7.5%, about 10%, about 11%, about 11.5%, about 12%, about 12.5%, about 13%, about 13.5%, about 14%, about 14.5%, about 15%, about

17.5%, about 20%, by weight, including any values or ranges therebetween, of Compound 1 or Compound 2, or a pharmaceutically salt thereof. In embodiments, the present disclosure provides pharmaceutical compositions for the topical treatment of pain comprising about 0.05% to about 10%, by weight, Compound 1 or Compound 2, or a pharmaceutically salt thereof, *e.g.*, about 0.05%, about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, about 5%, about 7.5%, or about 10%, by weight, including any values or ranges therebetween, of Compound 1 or Compound 2, or a pharmaceutically salt thereof.

[0021] In embodiments, the present disclosure provides pharmaceutical compositions for the topical treatment of pain comprising about 0.05%, about 0.1%, about 0.5% to about 5%, about 6% to about 10%, by weight, Compound 1 or Compound 2, or a pharmaceutically acceptable salt thereof, wherein the topical administration of an effective amount of the composition to a patient in need thereof provides a C_{max} of Compound 1 or Compound 2 of less than about 25 ng/mL.

[0022] In embodiments, the present disclosure provides pharmaceutical compositions comprising Compound 1 or Compound 2 and one or more of a permeation enhancer, a solvent, and a gelling agent. In embodiments, the "solvent" may function as a "permeation enhancer" (e.g., ethyl alcohol). In embodiments, the present disclosure provides topical compositions or formulations of Compound 1 or Compound 2. In embodiments, the formulation is a gel, ointment, cream, solution or suspension. In embodiments, the formulation contains an effective amount of Compound 1 or Compound 2 and a dermatologically acceptable carrier. In embodiments, the effective amount of Compound 1 or Compound 2 in the formulation is about 0.02% to about 20%, by weight. In embodiments, the effective amount of Compound 1 or Compound 2 in the formulation is about 0.05% to about 10%, by weight. In embodiments, the dermatologically acceptable carrier is a gelling agent, emollient agent, emulsifying agent, thickening agent, preservative, permeation enhancer, buffering agent, solvent, or a combination thereof. In embodiments, the emollient agent of the formulation is white petrolatum and mineral oil, the emulsifying agent is caprylocaproyl polyoxyl-8 glycerides, the thickening agent is glyceryl behenate and the solvent is DMSO and propylene carbonate.

[0023] In embodiments, emollient agents comprise vegetable oils, fats obtained from animals, semisolid hydrocarbons obtained from petroleum, and the like.

[0024] In embodiments, the present disclosure comprises one or more pharmaceutically acceptable carriers including for example, a surfactant, a polymeric thickening agent, a gelling agent, an emollient, an emulsifier, a buffering agent, a permeation enhancer, a solvent, and/or an

oleaginous ointment base. In embodiments, the carrier is a gelling agent, emollient agent, emulsifying agent, thickening agent, preservative, permeation enhancer, solvent, buffering agent, or a combination thereof.

[0025] In embodiments, the oleaginous ointment bases comprise white ointment, yellow ointment, cetyl esters wax, paraffin, petroltum, white petrolatum, white wax, yellow wax and the like and mixtures thereof. Non-limiting examples of polymers having thickening properties can include PEG-150 distearate, PEG-7 glyceryl cocoate, PEG 200 hydrogenated glyceryl palmitate, PEG-120 methyl glucose dioleate, carboxymethylene polymer, carboxyvinyl polymer, acrylates, Clo-C3O alkyl acrylate crosspolymers, and combinations thereof.

[0026] In embodiments, the emollient agent is white petrolatum. In embodiments, the emollient agent is mineral oil. In embodiments, the emollient age is a combination of white petrolatum and mineral oil.

[0027] In some embodiments, the formulation comprises a surfactant ranging from about 0.1% to about 20%, from about 0.1% to about 10%, from about 1% to about 10%, from about 2% to about 8%, or from about 3% to about 6% by weight in the formulation, including any values or ranges therebetween.

[0028] In some embodiments, the formulation comprises a thickener ranging from about 0.1% to about 20%, from about 0.1% to about 10%, from about 1% to about 10%, from about 1% to about 8%, from about 1% to about 5%, or from about 1% to about 3% by weight in the formulation, including any values or ranges therebetween.

[0029] In embodiments, the formulation comprises polymer(s) having surfactant or emulsifying properties.

[0030] In embodiments, polymers having surfactant or emulsifying properties comprise hydrophobically modified polyacrylic acid (commercially under the tradename Pemulen™ TR-I and TR-2 by Lubrizol Corp.), water-soluble or water-swellable copolymers based on acrylamidoalkyl sulfonic acid and cyclic N-vinylcarboxamides (commercially available under the tradename Aristoflex® AVC by Clariant Corporation); water-soluble or water-swellable copolymers based on acrylamidoalkyl sulfonic acid and hydrophobically modified methacrylic acid (commercially available under the tradename Aristo ex® HMB by Clariant Corporation) and a homopolymer of acrylamidoalkyl sulfonic acid (commercially available under the tradename Granthix APP by Grant Industries, Inc).

[0031] In embodiments, the polymers having surfactant or emulsifying properties comprise hydrophobically-modified, crosslinked, anionic acrylic copolymers. In embodiments, hydrophobically-modified, crosslinked, anionic acrylic copolymers comprise random polymers, block polymers, star polymers, graft polymers, and the like. In embodiments, the hydrophobically modified, crosslinked, anionic acrylic copolymer may be synthesized from at least one acidic monomer and at least one hydrophobic ethylenically unsaturated monomer. In embodiments, the acidic monomers comprise those ethylenically unsaturated acid monomers that may be neutralized by a base. In embodiments, the hydrophobic ethylenically unsaturated monomers comprises a hydrophobic chain having a carbon chain length of at least about 3 carbon atoms.

[0032] In embodiments, the compositions of the present disclosure comprise a surfactant, wherein the surfactant is a polymer. In embodiments, the formulation comprises about 0.1% to about 10%, by weight, a surfactant.

[0033] In embodiments, the compositions of the present disclosure comprise a thickening agent, wherein the thickening agent is a polymer. In embodiments, the compositions comprises about 0.1%-about 10%, by weight, a thickening agent.

Permeation Enhancer

[0034] In embodiments, the compositions of the present disclosure comprise a permeation enhancer which increases in the permeability of the skin to rise the rate at which the drug permeate into the skin. In embodiments, the compositions comprise about 5% to about 80%, by weight, a permeation enhancer, *e.g.*, about 5%, about 10%, about 15%, about 20%, about 22 %, about 24 %, about 25%, about 26 %, about 28 %, about 30%, about 32 %, about 34 %, about 35%, about 36 %, about 38 %, about 40%, about 42 %, about 44 %, about 45%, about 46 %, about 48 %, about 50%, about 52 %, about 54 %, about 55%, about 56 %, about 58 %, about 60 %, about 62 %, about 64 %, about 65%, about 66 %, about 68 %, about 70%, about 75%, or about 80%, by weight, a permeation enhancer, including all values and ranges therebetween. In embodiments, the compositions comprise a permeation enhancer at about 20 % to about 60 %, by weight. In embodiments, the compositions comprise a permeation enhancer at about 50 %, by weight.

[0035] In embodiments, the permeation enhancer comprises volatile organic solvents (*e.g.*, alcohols such as ethanol), nonvolatile organic solvents (*e.g.*, amides such as pyrrolidones; polyol ethers such as glycol ethers; polyols such as glycols; and derivatives thereof), and mixtures thereof.

[0036] In embodiments, the permeation enhancer comprises fatty acids, fatty acid esters, fatty alcohols, terpenes, glycols and glycol esters, 1,3-dioxolanes, macrocylic ketones containing at least 12 carbon atoms, oxazolidinones and oxazolidinone derivatives, alkyl-2-(N,N-disubstituted amino)-alkanoate esters, (N,N-disubstituted amino)-alkanol alkanoates and mixtures thereof.

[0037] In embodiments, the permeation enhancer is propylene glycol, polyethylene glycol of average molecular weight from 100 to 4000, diethylene glycol monoethyl ether, Transcutol®, Polysorbate 80, polyoxylglycerides, Labrasol® (caprylocaproyl polyoxyl-8 glyceride), diethyl sebacate, diisopropyl adipate, dimethyl isosorbide, isosorbide dimethyl ether, dimethyl sulfoxide, ethyl alcohol, Tween 80, Laureth-4, butanediol, polyethylene glycol monolaurate, diethylene glycol monoethyl ether, dimethylsulfoxide, decylmethylsulfoxide, lauric acid, oleic acid, valeric acid, isopropyl myristate, isopropyl palmitate, methyl propionate, ethyl oleate, glycerol monooleate, oleyl alcohol, oleic acid, D-α-Tocopherol polyethylene glycol 1000 succinate (also known as Tocofersolan or tocophersolan or TPGS), or mixtures thereof.

[0038] In embodiments, the permeation enhancer is isopropyl myristate.

[0039] In embodiments, the permeation enhancer is isopropyl myristate and Transcutol®.

[0040] In embodiments, the permeation enhancer is dimethyl isosorbide and oleic acid.

Solvent

[0041] In embodiments, compositions of the present disclosure further comprise a solvent. In embodiments, the compositions comprise about 20% to about 70%, by weight, a solvent, *e.g.*, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, or about 70%, by weight, a solvent, including all values and ranges therebetween. In embodiments, the compositions comprise about 5% to about 80%, by weight, a solvent, *e.g.*, about 5%, about 10%, about 15%, about 20%, about 22 %, about 24 %, about 25%, about 26 %, about 28 %, about 30%, about 32 %, about 34 %, about 35%, about 36 %, about 38 %, about 40%, about 42 %, about 44 %, about 45%, about 46 %, about 48 %, about 50%, about 52 %, about 54 %, about 55%, about 56 %, about 58 %, about 60 %, about 62 %, about 64 %, about 65%, about 66 %, about 68 %, about 70%, about 75%, or about 80%, by weight, a solvent, including all values and ranges therebetween. In embodiments, the compositions comprise a solvent at about 30 % to about 60 %, by weight. In embodiments, the compositions comprise a solvent at about 50 %, by weight.

[0042] In embodiments, the solvent is ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (such as cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures thereof.

[0043] In embodiments, the solvent is ethyl alcohol.

Gelling Agent

[0044] In embodiments, compositions of the present disclosure comprise a gelling agent. In embodiments, the compositions comprise about 1% to about 10%, by weight, a gelling agent, *e.g.*, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, about 5%, about 5.5%, about 6%, about 6.5%, about 7%, about 7.5%, about 8%, about 8.5%, about 9%, about 9.5%, or about 10%, by weight, a gelling agent, including all values and ranges therebetween. In embodiments, the compositions comprise a gelling agent at about 2 % to about 6 %, by weight. In embodiments, the compositions comprise a gelling agent at about 5 %, by weight.

[0045] In embodiments, the gelling agent is acacia, alginic acid, bentonite, carbomers, carboxymethyl cellulose, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, magnesium aluminum silicate, methylcellulose, poloxamers, polyvinyl alcohol, sodium alginate, tragacanth, xanthan gum, or mixtures thereof.

[0046] In embodiments, the gelling agent is ethylcellulose.

[0047] In embodiments, compositions of the present disclosure further comprise a permeation enhancer and a solvent, wherein the permeation enhancer is isopropyl myristate or ethyl alcohol, and the solvent is ethyl alcohol.

[0048] In embodiments, compositions of the present disclosure comprise a permeation enhancer, gelling agent, and a solvent, wherein the permeation enhancer is isopropyl myristate, the gelling agent is ethyl cellulose, and the solvent is ethyl alcohol.

[0049] In embodiments, the present disclosure provides a pharmaceutical composition comprising about 0.05% to about 10%, by weight, of Compound 1 or Compound 2, or a pharmaceutically acceptable salt thereof, about 20% to about 60%, by weight, of a permeation enhancer, about 35% to about 55%, by weight, of a solvent; and about 1% to about 10%, by weight, of a gelling agent.

[0050] In embodiments, the present disclosure provides a pharmaceutical composition comprising about 0.05% to about 10%, by weight, of Compound 1 or Compound 2, or a pharmaceutically acceptable salt thereof, about 20% to about 60%, by weight, of isopropyl myristate, about 35% to about 55%, by weight, of ethyl alcohol; and about 1% to about 10%, by weight, of ethyl cellulose.

[0051] In embodiments, the present disclosure provides a pharmaceutical composition comprising about 1%, by weight, of Compound 1 or Compound 2, or a pharmaceutically acceptable salt thereof, about 50% by weight, of isopropyl myristate, about 45% by weight, of ethyl alcohol; and about 5%, by weight, of ethyl cellulose.

[0052] In embodiments, compositions of the present disclosure are contained within a suitable container. In embodiments, the container is a pouch. In embodiments, the container is a tube. In some embodiment, the container is a jar. In some embodiment, the container is a bottle. In some embodiment, the container is a dispenser.

[0053] In embodiments, the formulations of the present disclosure are packaged for single dose administration, *e.g.*, as a single use pouch, or a single use tube, or a multiple use jar or bottle or dispenser.

[0054] In embodiments, the emollient is mineral oil, dimethicone, glycerin, isopropyl palmitate, propylene glycol, petrolatum, carnauba wax, cetyl alcohol, cetyl ester wax, cetostearyl alcohol, emulsifying wax, hydrous lanolin, lanolin, lanolin alcohols, microcrystalline wax, paraffin, stearic acid, stearyl alcohol, white wax, yellow wax, squalane, or mixtures thereof.

[0055] In embodiments, the topical formulation is the form of an ointment. In embodiments, the formulation comprises about 0.05% to about 10% of Compound 1 or Compound 2, about 1% to about 10% or from about 4% to about 5% of a solvent, about 1% to about 10% (*e.g.*, about 5%) of a surfactant (*e.g.*, Labrasol or caprylocaproyl polyoxyl-8 glycerides), about 1% to about 10% (*e.g.*, about 2%) of a thickening agent (*e.g.*, Compritol 888 ATO or glyceryl dibehenate), and about 70% to about 80% of an ointment base.

[0056] In some embodiments, the formulation comprises about 20% to about 90%, by weight, the ointment base.

[0057] In embodiments, the one or more pharmaceutically acceptable carriers comprise an ointment bases comprising white ointment, yellow ointment, cetyl esters wax, paraffin, petroltum, white petrolatum, white wax, yellow wax, or mixtures thereof. In some embodiments, one or more

pharmaceutically acceptable carriers are prepared in a separate mixture or solution, which is then combined with the solution of Compound 1 or Compound 2. In some embodiments, the solvent is ethanol, N-Methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), propylene glycol, dimethyl isosorbide (DMI), glycerin, propylene carbonate, or mixtures thereof.

[0058] In embodiments, the solvent for dissolving the therapeutic agent (e.g., Compound 1 or Compound 2) comprises one, two, three or more organic components (e.g. ethanol, DMSO, propylene carbonate). The agent can also be dissolved in one component with subsequent addition of an additional component.

Methods

[0059] In one aspect, the present disclosure provides methods of treating pain in a patient need thereof, comprising topically administering an effective amount of a composition described herein.

[0060] In embodiments, the composition is administered once a day.

[0061] In embodiments, the composition is administered twice a day.

[0062] In embodiments, the composition is administered three times a day.

[0063] In embodiments, the composition is administered 1-3 times a day or more a day, or as needed. In embodiments, the composition is administered once every two, three, four days, or as needed. The actual amount and frequency of administering the composition may depend on the specific disease conditions and can be determined by one of ordinary skill in the art (e.g. a dermatologist, a pain specialist or physician) without undue experiment.

[0064] In embodiments, the methods comprise topical application of the formulation disclosed herein on the skin area to be treated once or twice, or as needed daily to provide targeted, localized, effective concentrations of agents. The skin area may be on any part of a subject's body such as face, torso, and limbs. In embodiments, the subject is a human. The exact dosage and frequency of administration may depend on the subject's specific condition and the agent. One skilled in the art can determine the suitable administration regimen in view of the formulation disclosed herein and the knowledge available in the relevant medical field (e.g. a pain specialist or physician).

[0065] In embodiments, the dermal exposure of a single administration of the composition lasts for about 4 hours to about 6 hours, *e.g.*, about 4 hours, about 4.5 hours, about 5 hours, about 5.5 hours, or about 6 hours, including all values and ranges therebetween.

[0066] In embodiments, the pain is neuropathic pain.

[0067] In embodiments, administration of the composition provides a significant reduction in pain caused by a human disease selected from cancer induced pain, chemotherapy-induced pain, cancer-treatment induced pain, acute pain, chronic pain, neuropathic pain, inflammatory pain, radicular pain, sciatica, back pain, head pain, neck pain, severe or intractable pain, post-surgical pain, visceral pain, osteoarthritis pain, peripheral neuropathy, nociceptive pain, breakthrough pain, migraine, angina, vascular disease, arteriosclerosis, sleep disorders, metabolic disorders. gastrointestinal disease, schizophrenia, drug dependence, tinnitus, dementia, asthma, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, neurodegenerative disorders, arthritis, anxiety, depression, myotonia, arrythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, postherpetic neuralgia, diabetic neuropathy, contraception, nervous system injury, seizure, convulsion, Huntington's chorea, Alzheimer' disease, autoimmune disease, tremor, Parkinson's diseases, amyotrophic lateral sclerosis (ALS), retinopathy, neoplasm, inflammation, cranial neuropathy, type 1 or type 2 diabetes, hyperaldosteronemia, preterm labor, urinary incontinence, brain aging, and a combination thereof.

[0068] In embodiments, the topical administration of a Compound 1-containing composition or a Compound 2-containing composition disclosed herein reduces the average or the sum of daily Numeric Pain Rating Scale (NPRS) score in a patient for at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 70%, at least 80%, at least 90%, about 10% to about 90%, about 20% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%, or any values or ranges therebetween, compared to the NPRS score of the patient prior to treatment.

[0069] In embodiments, the topical administration of a Compound 1-containing composition or a Compound 2-containing composition disclosed herein reduces the short-form McGill Pain Questionnaire score (SF-MPQ-2) in a patient for at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 70%, at least 80%, at least 90%, about 10% to about 90%, about 20% to about 80%, about 30% to about 70%,

about 30% to about 60%, or about 30% to about 50%, or any values or ranges therebetween, compared to the SF-MPQ-2 score of the patient prior to treatment.

[0070] In embodiments, the topical administration of a Compound 1-containing composition or a Compound 2-containing composition disclosed herein reduces the Pain and Sleep Questionnaire (PSQ-3) in a patient for at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 70%, at least 80%, at least 90%, about 10% to about 90%, about 20% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%, or any values or ranges therebetween, compared to the PSQ-3 score of the patient prior to treatment.

[0071] In embodiments, the topical administration of a Compound 1-containing composition or a Compound 2-containing composition disclosed herein reduces the Patient Global Impression of Change (PGIC) in a patient for at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 70%, at least 80%, at least 90%, about 10% to about 90%, about 20% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%, or any values or ranges therebetween, compared to the PGIC score of the patient prior to treatment.

[0072] In embodiments, the topical administration of a Compound 1-containing composition or a Compound 2-containing composition disclosed herein reduces the frequency of use and dose of rescue medication during treatment period in a patient for at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 70%, at least 80%, at least 90%, about 10% to about 90%, about 20% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%, or any values or ranges therebetween, compared to the patient prior to treatment.

[0073] In embodiments, the topical administration of a Compound 1-containing composition or a Compound 2-containing composition disclosed herein reduces the cutaneous hypersensitivity measured by quantitative sensory tests (QST) in a patient for at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 70%, at least 80%, at least 90%, about 10% to about 90%, about 20% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%, or any values or ranges therebetween, compared to the QST score of the patient prior to treatment.

[0074] In embodiments, the topical administration of a Compound 1-containing composition or a Compound 2-containing composition disclosed herein reduces intra- and sub-

epidermal markers of sensory and nociceptor nerve fibres determined in the skin biopsy in a patient for at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 70%, at least 80%, at least 90%, about 10% to about 90%, about 20% to about 80%, about 30% to about 70%, about 30% to about 60%, or about 30% to about 50%, or any values or ranges therebetween, compared to the patient prior to treatment.

[0075] In embodiments, the present disclosure provides methods of managing pain in a patient need thereof, comprising topically administering an effective amount of a composition described herein.

[0076] From the foregoing, it will be appreciated that specific embodiments of the invention have been described herein for purposes of illustration, but that various modifications may be made without deviating from the scope of the invention.

EXAMPLES

[0077] The disclosure now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present disclosure and are not intended to limit the invention.

Example 1: Formulations

[0078] Following optimization, a 23 mg of Compound 1 formulation having the characteristics shown in Table 1 was prepared. The formulation is a liquid gel including the drug substance, Compound 1, at 23 mg (1.15 % w/w) along with isopropyl myristate NF (50% v/v), dehydrated alcohol USP (i.e., ethyl alcohol, 50% v/v), and ethylcellulose NF (4% w/v), filled into a pouch.

Table 1. Unit Composition

Component	Composition			Function
	mg/pouch without overfill	mg/pouch with 20% overfill	wt%	
Compound 1	23.0	27.6	1.15	Drug Substance
Isopropyl Myristate NF	977.0	1172.4	48.85	Permeation Enhancer
Dehydrated Alcohol USP	908.0	1089.6	45.4	Solvent/Permeation Enhancer
Ethylcellulose NF	92.0	110.4	4.60	Gelling Agent

Total	**2000**	**2400**	**100**

Example 2: Pharmacokinetic Data and Safety Evaluation

[0079] Compound 1 gel was applied topically as a thin layer to a pre-selected demarcated appropriate skin area (and if necessary to an additional area) of the body, primarily on the upper back. The dose application was about 8.7 mg/cm^2 (10 µL/cm^2) of 1.15% (w/w) Compound 1 gel (equating to 0.1 mg/cm^2 of Compound 1) or placebo gel. For each application, the drug remained on the application site for 6 hours ("application-period") before removal. The dose levels were increased by enlarging the application skin area, starting from 100 cm^2 and up to 400 cm^2, corresponding to about 0.62% and 2.47% of the body surface area [BSA] (based on a 60-kg human), respectively.

[0080] In a randomized, double-blind, and placebo-controlled single ascending dose study of Compound 1 in healthy human subjects, sixteen (16) subjects participated in the study in 2 cohorts, 12 of whom were exposed to one dose of Compound 1 (10 mg or 40 mg) and 4 to matching placebo, refer the Table 2 below. The subjects enrolled in the study were exclusively White, Hispanic or Latino, and predominantly female (87.5%).

Table 2. Subject Exposure to Study Product After Single Ascending Doses

Drug	N	Analysis Set	Total Dose per Subject
Compound 1 Cohort 1	6	Per-Protocol	10 mg Compound 1; 0.87 g of 1.15% Compound 1 gel
Compound 1 Cohort 2	6	Per-Protocol	40 mg Compound 1; 3.48 g of 1.15% Compound 1 gel
Placebo	4	Per-Protocol	0

[0081] The PK analysis could not be conducted because no quantifiable concentrations for Compound 1 were observed for all of the 112 samples tested that were submitted.

[0082] Compound 1 gel was shown to be safe and well tolerated following single topical doses of 10 and 40 mg over 100 cm^2 and 400 cm^2, respectively. All Treatment emergent adverse events (TEAEs) were mild, transient, and unrelated to the administration of Compound 1. There were no clinically significant changes in clinical laboratory findings, vital signs, ECG results, and local skin appearance or condition. No SAEs or serious treatment emergent adverse events (TESAEs) occurred.

[0083] In a randomized, double-blind, and placebo-controlled multiple ascending dose study of Compound 1 in healthy human subjects, sixteen (16) subjects participated in the study in 2 cohorts, 12 of whom were exposed to nine doses of Compound 1 (10 mg or 40 mg) over 5 days and 4 to matching placebo, refer the Table 3 below. All of the subjects' ethnicity was Hispanic or Latino with an approximate 80%/20% split in racial background that indicated a higher percentage of White subjects than African American subjects.

Table 3. Subject Exposure to Study Product After Multiple Ascending Doses.

Exposure for each subject	Topical Dose Administered in 9 applications	Total Exposure (g)
Cohort 1	10 mg (0.87 g Compound 1 gel)	7.83 g
Cohort 2	40 mg (3.48 g Compound 1 gel)	31.32 g

[0084] There were no PK evaluations for the low dose (10 mg) regimen because no quantifiable concentrations for Compound 1 were observed. The high dose group (40 mg) also showed very low systemic exposures with all plasma concentrations for Compound 1 less than 6 ng/mL.

[0085] Compound 1 gel was well-tolerated when applied to either 100 cm^2 or 400 cm^2 twice a day for 9 doses. TEAEs other than at the application site were not considered related to study drug. All TEAEs were mild and resolved without treatment. Findings at the application site were none or minimal for all but 2 subjects for all characteristics. These two subjects showed moderate erythema which resolved completely by study end.

Example 3: Efficacy studies of orally administered Compound 1 treating pain *in vivo*

[0086] The efficacy of orally administered Compound 1 was assessed by using the following nociceptive, neuropathic, and inflammatory pain animal models: 1) carrageenan-induced pain rat model, 2) formalin-induced pain rat model, 3) chronic construction injury (CCI)-induced pain rat model, 4) spinal nerve ligation (CNL)-induced pain rat model, 5) bone cancer-induced pain rat model, 6) complete Freund's adjuvant (CFA)-induced inflammatory pain rat model, 7) Zymosan-induced lower back pain rat model, and 8) post-operative pain model rat model. For each animal, 0.1 mg/kg-2 mg/kg of Compound 1 formulation of Example 1 or Compound 2 formulation (at 1 mg/kg – 10 mg/kg) was orally administered. All the tested animal models showed statistically significant analgesic effects as compared to vehicle treated control rats: 1) reversing injured hind paw pressure deficit, 2) reversing the frequencies of spontaneous flinches in the injured hindpaw, 3) reducing mechanical allodynia, 4) reducing the mechanical

allodynia in the SNL neuropathic pain model, 5) inhibiting the tumor induced allodynia, 6) reducing hypersensitivity to tactile stimuli and thermal hyperalgesia in the injured paw, 7) attenuating hypersensitivity to tactile stimuli, and 8) providing analgesic effects in the post-operative pain model in rats.

Example 4: Efficacy studies of topically administered Compound 1 treating pain *in vivo*

[0087] The carrageenan-induced pain model in rats were used for the study to assess the analgesic efficacy of Compound 1 *in vivo*. Compound 1 formulation of Example 1 was topically administered to the injured hind paw at a topical dose, *e.g.*, 0.1 mg/kg (about 2.9 μg/cm^2), 0.3 mg/kg (about 8.7 μg/cm^2), or 2 mg/kg (about 57.6 μg/cm^2). A dose-dependent, statistically significant analgesic efficacy was observed following administration. Low levels of plasma concentrations (less than 35 ng/mL) were observed in the tested animals, demonstrating topical (and not systemic) effects of Compound 1 observed in this study.

Example 5: A randomized, double-blind, placebo-controlled study to evaluate analgesic efficacy, safety, and tolerability of repeated doses of topical Compound 1 administration in patients with chemotherapy-induced peripheral neuropathy (CIPN).

[0088] Phase 2a double-blind, randomized, crossover repeated-dose trial of topical Compound 1 in cancer patients in remission, diagnosed with CIPN will be conducted. In this study, up to 46 mg (or any appropriate doses less than 80 mg/day maximum administered dose (MAD) determined in the Phase 1 study) of Compound 1 will be topically administered to Compound 1 tested group participants.

[0089] The primary objectives of the study are to assess the analgesic efficacy of repeated topical doses of Compound 1 in patients with CIPN, and to assess the safety and tolerability of repeated topical doses of Compound 1 in patients with CIPN. The secondary objective of the study is to assess the pharmacodynamics (PD) of repeated topical doses of Compound 1 in patients with CIPN.

[0090] The primary endpoint is Numeric Pain Rating Scale (NPRS). The secondary endpoints include Short-form McGill Pain Questionnaire (SF-MPQ-2), sleep interference scores (PSQ-3), quantitative sensory tests (QST), skin biopsies (in ≥ 8 participants),Patient global impression of change (PGIC), frequency of use and dose of rescue medication during treatment period, reduction in cutaneous hypersensitivity (light touch perception, and thermal and vibration

perception thresholds) as measured by quantitative sensory tests (QST), and intra- and sub-epidermal markers of sensory and nociceptor nerve fibres.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described. Rather, the scope of the present invention is defined by the claims which follow. It should further be understood that the above description is only representative of illustrative examples of embodiments. The description has not attempted to exhaustively enumerate all possible variations. The alternate embodiments may not have been presented for a specific portion of the invention, and may result from a different combination of described portions, or that other un-described alternate embodiments may be available for a portion, is not to be considered a disclaimer of those alternate embodiments. It will be appreciated that many of those un-described embodiments are within the literal scope of the following claims, and others are equivalent.