IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Barrow, Robert et al Confirmation No.: 1064

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Entitled: Psychedelics for Treatment of Pain

THIRD-PARTY PRE-ISSUANCE SUBMISSION

Examiner:

The following documents, which are also identified in the Form PTO/SB/429 filed herewith, are submitted for your consideration as being of potential relevance to the examination of the present application:

1. Int'l Pat. App. Pub. No. WO/2021/175816 "Compounds for Use in a Method of Treating, Preventing, and/or Reducing the Symptoms of Pain" (Published September 10, 2021)
2. Int'l Pat. App. Pub. No. WO/2022/011350 "Method of Treatment for Psilocybin or Psilocin Infusion" (Published July 12, 2021)
3. Castellanos (2020) Chronic pain and psychedelics: a review and proposed mechanism of action Reg Anesth Pain Med. 45(7):486-494
4. Hutten (2019) "Self-Rated Effectiveness of Microdosing With Psychedelics for Mental and Physical Health Problems Among Microdosers" Front Psychiatry. 10:672
5. Int'l Pat. App. Pub. No. WO/2021/209815 "Transdermal Micro-Dosing Delivery of Psychedelics Derivatives" (Published October 21, 2021)
6. Int'l Pat. App. Pub. No. WO/2020/181194 "Compositions and Methods of Use Comprising Substances with Neural Plasticity Actions Administered at Non-Psychedelic/Psychotomimetic Dosages and Formulations" (Published September 10, 2020)
7. Int'l Pat. App. Pub. No. WO/2022/212854 "Methods and Compositions Relating to Psychedelics and Serotonin Receptor Modulators" (Published November 6, 2022)
8. Int'l Pat. App. Pub. No. WO/2022/225884 "Deuterated Derivatives of Psychedelic Compounds and Uses Thereof" (Published October 27, 2022)

1. A method of treating pain, including the steps of: administering an effective amount of a psychedelic to an individual; and treating pain in the individual.	1. Int'l Pat. App. Pub. No. WO/2021/175816 "Compounds for Use in a Method of Treating, Preventing, and/or Reducing the Symptoms of Pain" (Published September 10, 2021)

	From **Claim 1 "**Compound for use in a method of treating, preventing or reducing the symptoms of **pain**, where in the compound is administered to a subject in an amount of 2 to 50 mcg per day, and the compound is a **lysergamide** or a pharmaceutically acceptable salt thereof" 2. Int'l Pat. App. Pub. No. WO/2022/011350 "Method of Treatment for Psilocybin or Psilocin Infusion" (Published July 12, 2021) From **Abstract** "Methods for treatment for patients suffering from disease or condition are contemplated as including an administration of an intravenous infusion of a pharmaceutically effective amount of **psilocybin or psilocin**. The intravenous infusion of psilocybin or psilocin may include an additional compound such as a benzodiazepine, preferably lorazepam, administered via a continuous intravenous infusion. Such methods may be seen to better alleviate the symptoms of psychological conditions, neurological injuries, **pain**, or inflammatory condition, and may result in reduced need for other medications."
2. The method of claim 1, wherein the pain is a type chosen from the group consisting of acute, chronic, nociceptive, neuropathic, inflammatory, and functional.	3. Castellanos (2020) Chronic pain and psychedelics: a review and proposed mechanism of action Reg Anesth Pain Med. 45(7):486-494 From **Page 486 "**There is also evidence that psychedelic drugs may possess antinociceptive effects in **chronic pain conditions.**" 1. Int'l Pat. App. Pub. No. WO/2021/175816 "Compounds for Use in a Method of Treating, Preventing, and/or Reducing the Symptoms of Pain" (Published September 10, 2021)

	From **Claim 1 "**Compound for use in a method of treating, preventing or reducing the symptoms of **pain**, where in the compound is administered to a subject in an amount of 2 to 50 pg per day, and the compound is a **lysergamide** or a pharmaceutically acceptable salt thereof" From **Claim 2 "**The compound for use according to claim 1, wherein the compound is **lysergic acid diethylamide (LSD)** or a pharmaceutically acceptable salt thereof." From **Claim 5** "The compound for use according to any one of claims 1 to 4, wherein the pain is an **acute pain** or a **chronic pain**" From **Claim 6** "6. The compound for use according to any one of claims 1 to 5, wherein the pain is selected from head pain such as cluster headache and migraine; visceral pain such as irritable bowel syndrome (IBS) and menstrual cramps; somatic pain such as postoperative pain; **neuropathic pain** such as fibromyalgia, central pain syndrome, complex regional pain syndrome, trigeminal neuralgia, posttraumatic neuralgia, peripheral neuropathy and herpetic/postherpetic neuralgia; **inflammatory pain** such as osteoarthritis, rheumatoid arthritis and atherosclerosis; **functional pain** such as psychogenic/psychosomatic pain and phantom limb pain; and pain in advanced and progressive diseases such as pain in acquired immune deficiency syndrome (AIDS), cancer, multiple sclerosis (MS) and Crohn's disease." 8. Int'l Pat. App. Pub. No. WO/2022/225884 "Deuterated Derivatives of Psychedelic Compounds and Uses Thereof" (Published October 27, 2022) From **Paragraph [003] "**The present invention relates to compositions (e.g., pharmaceutical compositions) comprising deuterated derivatives of certain naturally-occurring and synthetic **psychedelic compounds**."

	From **Paragraph [00101] "**In certain embodiments, the disease is a painful condition. A "painful condition" includes **neuropathic pain** (e.g., peripheral neuropathic pain), central pain, deafferentation pain, **chronic pain** (e.g., chronic nociceptive pain, and other forms of chronic pain such as post-operative pain, e.g., pain arising after hip, knee, or other replacement surgery), pre-operative pain, stimulus of nociceptive receptors (**nociceptive pain**), **acute pain** (e.g., phantom and transient acute pain), noninflammatory pain, **inflammatory pain**, pain associated with cancer, wound pain, bum pain, postoperative pain, pain associated with medical procedures, pain resulting from pruritus, painful bladder syndrome, pain associated with premenstrual dysphoric disorder and/or premenstrual syndrome, pain associated with chronic fatigue syndrome, pain associated with pre-term labor, pain associated with withdrawal symptoms from drug addiction, joint pain, arthritic pain (e.g., pain associated with crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis or Reiter's arthritis), lumbosacral pain, musculo-skeletal pain, headache, migraine, muscle ache, lower back pain, neck pain, toothache, dental/maxillofacial pain, visceral pain and the like." 2. Int'l Pat. App. Pub. No. WO/2022/011350 "Method of Treatment for Psilocybin or Psilocin Infusion" (Published July 12, 2021) From **Claim 10** "A method of treating a disease or condition in a subject in need thereof, the method comprising intravenously administering to the subject a pharmacologically effective amount of (i) **psilocybin or psilocin**, or a pharmaceutically acceptable salt thereof, and (ii) a benzodiazepine, each in an amount that

	together is effective for the treatment of the disease or condition." From **Claim 46** "The method of any one of claims 1 -38, wherein the disease or condition is a neurological injury, an inflammatory condition, or **pain**." From **Claim 52** "The method of claim 46, wherein the disease or condition **is chronic pain**."
3. The method of claim 1, wherein the pain is caused by a physical state in the individual's body.	3. Castellanos (2020) Chronic pain and psychedelics: a review and proposed mechanism of action Reg Anesth Pain Med. 45(7):486-494 From **Page 490 "**The earliest published studies on psychedelics and analgesia are works from Dr Eric Kast in the mid-1960s on **analgesic response to LSD for cancer pain**. In these studies, LSD not only acutely outperformed 2mg of PO hydromorphone or 100 mg of PO meperidine but also produced analgesia that persisted for an average of 3 weeks after LSD administration." 1. Int'l Pat. App. Pub. No. WO/2021/175816 "Compounds for Use in a Method of Treating, Preventing, and/or Reducing the Symptoms of Pain" (Published September 10, 2021) From **Claim 6** "The compound for use according to any one of claims 1 to 5, wherein the pain is selected from **head pain** such as cluster headache and migraine; **visceral pain** such as irritable bowel syndrome (IBS) and menstrual cramps; **somatic pain** such as postoperative pain; neuropathic pain such as fibromyalgia, central pain syndrome, complex regional pain syndrome, trigeminal neuralgia, posttraumatic neuralgia, peripheral neuropathy and herpetic/postherpetic neuralgia; inflammatory pain such as osteoarthritis, rheumatoid arthritis and atherosclerosis; functional pain such as

	psychogenic/psychosomatic pain and phantom limb pain; and pain in advanced and progressive diseases such as pain in acquired immune deficiency syndrome (AIDS), cancer, multiple sclerosis (MS) and Crohn's disease." 8. Int'l Pat. App. Pub. No. WO/2022/225884 "Deuterated Derivatives of Psychedelic Compounds and Uses Thereof" (Published October 27, 2022) From **Paragraph [00101]** "In certain embodiments, the disease is a painful condition. A "painful condition" includes neuropathic pain (e.g., peripheral neuropathic pain), central pain, deafferentation pain, chronic pain (e.g., chronic nociceptive pain, and other forms of chronic pain such as post-operative pain, e.g**., pain arising after hip, knee, or other replacement surgery**), pre-operative pain, stimulus of nociceptive receptors (nociceptive pain), acute pain (e.g., phantom and transient acute pain), noninflammatory pain, inflammatory pain**, pain associated with cancer**, **wound pain, bum pain**, postoperative pain, pain associated with medical procedures, **pain resulting from pruritus**, **painful bladder syndrome**, **pain associated with premenstrual dysphoric disorder and/or premenstrual syndrom**e, pain associated with chronic fatigue syndrome, **pain associated with pre-term labor**, pain associated with withdrawal symptoms from drug addiction, **joint pain**, **arthritic pain** (e.g., pain associated with crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis or Reiter's arthritis), **lumbosacral pain**, **musculo-skeletal pain**, **headache**, **migraine**, **muscle ache**, **lower back pain**, **neck pain**, **toothache**, **dental/maxillofacial pain**, **visceral pain** and the like."

	2. Int'l Pat. App. Pub. No. WO/2022/011350 "Method of Treatment for Psilocybin or Psilocin Infusion" (Published July 12, 2021) From **Claim 10** "A method of treating a disease or condition in a subject in need thereof, the method comprising intravenously administering to the subject a pharmacologically effective amount of (i) **psilocybin or psilocin**, or a pharmaceutically acceptable salt thereof, and (ii) a benzodiazepine, each in an amount that together is effective for the treatment of the disease or condition." From **Claim 46** "The method of any one of claims 1 -38, wherein the disease or condition is a neurological injury, an inflammatory condition, or **pain**." From **Claim 53** "The method of claim 52, wherein the chronic pain results **from post-operative pain, tension headaches, chronic lower back pain, fibromyalgia, nephropathy, multiple sclerosis, shingles, complex regional pain syndrome, cephalic pain, or sciatica**."
4. The method of claim 1, wherein the pain is caused by an emotional state in the individual's body.	3. Castellanos (2020) Chronic pain and psychedelics: a review and proposed mechanism of action Reg Anesth Pain Med. 45(7):486-494 From **Page 489 "**Studies with single session administrations of **LSD, psilocybin** and **MDMA** have shown alleviation of **anxiety and depression** which may persist for weeks, or even months." From **Claim 6** "The compound for use according to any one of claims 1 to 5, wherein the pain is selected from head pain such as cluster headache and migraine; visceral pain such as irritable bowel syndrome (IBS) and menstrual cramps; somatic pain such as postoperative pain; neuropathic pain such as fibromyalgia, central pain syndrome, complex

	regional pain syndrome, trigeminal neuralgia, posttraumatic neuralgia, peripheral neuropathy and herpetic/postherpetic neuralgia; inflammatory pain such as osteoarthritis, rheumatoid arthritis and atherosclerosis; **functional pain such as psychogenic/psychosomatic pain** and **phantom limb pain**; and pain in advanced and progressive diseases such as pain in acquired immune deficiency syndrome (AIDS), cancer, multiple sclerosis (MS) and Crohn's disease."
5. The method of claim 1, wherein the psychedelic is chosen from the group consisting of lysergic acid diethylamide (LSD), psilocybin, psilocin, mescaline, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), dimethyltryptamine (DMT), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamie (DOB), salts thereof, tartrates thereof, solvates thereof, isomers thereof, analogs thereof, and homologues thereof.	1. Int'l Pat. App. Pub. No. WO/2021/175816 "Compounds for Use in a Method of Treating, Preventing, and/or Reducing the Symptoms of Pain" (Published September 10, 2021) From **Claim 2 "**The compound for use according to claim 1, wherein the compound is **lysergic acid diethylamide (LSD)** or a pharmaceutically acceptable salt thereof." 2. Int'l Pat. App. Pub. No. WO/2022/011350 "Method of Treatment for Psilocybin or Psilocin Infusion" (Published July 12, 2021) From **Claim 10** "A method of treating a disease or condition in a subject in need thereof, the method comprising intravenously administering to the subject a pharmacologically effective amount of (i) **psilocybin or psilocin**, or a pharmaceutically acceptable salt thereof, and (ii) a benzodiazepine, each in an amount that together is effective for the treatment of the disease or condition." From **Claim 46** "The method of any one of claims 1 -38, wherein the disease or condition is a neurological injury, an inflammatory condition, or **pain**." 7. Int'l Pat. App. Pub. No. WO/2022/212854 "Methods and Compositions Relating to

	Psychedelics and Serotonin Receptor Modulators" (Published November 6, 2022) From **Claim 4** "The composition of claim 1, wherein the psychedelic is selected from **psilocybin**, **psilocin**, baeocystin, norbaeocystin, lisurgide, **LSD**, **dimethyltryptamine**, carboxamindotryptamine, ibogaine, tabemanthalog, 3,4-methylenedioxy-methamphetamine (MDMA), 1-acetyl LSD, O-acetyl psilocin, **mescaline (3,4,5-trimethoxy phenethylamine)**, … **or a pharmaceutically acceptable salt, solvate, metabolite, deuterated analogue, derivative, prodrug, or combinations thereof**." From **Paragraph [0005]** "In some embodiments, the psychedelic is a phenethylamine or a tryptamine, or a pharmaceutically acceptable salt, solvate, metabolite, deuterated analogue, derivative, or prodrug thereof. In some embodiments, the phenethylamine or the tryptamine is selected from the group consisting of… **2,5-dimethoxy-4-iodophenethylamine** … **2,5-dimethoxy-4-bromoamphetamine** … **5-meo-DMT** … **or a pharmaceutically acceptable salt, solvate, metabolite, deuterated analogue, derivative, prodrug, or combinations thereof**."
6. The method of claim 1, wherein said treating step is further defined as providing a psychological effect and a direct neural effect to the individual.	4. Hutten (2019) "Self-Rated Effectiveness of Microdosing With Psychedelics for Mental and Physical Health Problems Among Microdosers" Front Psychiatry. 10:672 From **Page 1 "**As of the last few years, there has been an increasing visibility and interest in the use of low doses of **psychedelics**, such as lysergic acid diethylamide (LSD) and psilocybin, for beneficial health-related purposes. Referred to as "microdosing," users report consuming about one tenth of a recreational dose, to enhance daily functions, without inducing a profound altered state of consciousness. While the primary motivation

	to microdose is indeed to enhance performance, including creativity and mental concentration, it is also reported to be used to alleviate **psychological and physical symptoms**, such as anxiety and headache."
7. The method of claim 1, wherein said administering step is further defined as administering the psychedelic in a form chosen from the group consisting of transdermal patches, modified-release oral dosage forms, extended release injection, implanted titration device, intranasal delivery forms, and sublingual delivery forms.	1. Int'l Pat. App. Pub. No. WO/2021/175816 "Compounds for Use in a Method of Treating, Preventing, and/or Reducing the Symptoms of Pain" (Published September 10, 2021) From **Page 14, lines 6-12** "The routes for administration (delivery) include one or more of **oral** (e.g. tablet, capsule, ingestable solution), **topical**, mucosal (e.g. nasal spray, aerosol for inhalation), **nasal**, **parenteral** (e.g. an **injectable** form), and **sublingual**. According to a preferred embodiment, the compound of the present invention is administered by topical administration, parenteral administration or mucosal administration, more preferably by mucosal administration such as intranasal administration, buccal administration or sublingual administration." 5. Int'l Pat. App. Pub. No. WO/2021/209815 "Transdermal Micro-Dosing Delivery of Psychedelics Derivatives" (Published October 21, 2021) From **Claim 1** "A **transdermal and/or topical pharmaceutical composition** comprising: about 0.1 % to about 20 % of an active agent selected from the group consisting of **psilocybin, psilocin, lysergic acid diethylamine (LSD),** and/or **ibogaine**, derivatives of these compounds, and combinations thereof.." From **Claim 7** "The pharmaceutical composition of any one of claims 1 to 6 which is formulated as a **transdermal patch**." 6. Int'l Pat. App. Pub. No. WO/2020/181194 "Compositions and Methods of Use

	Comprising Substances with Neural Plasticity Actions Administered at Non-Psychedelic/Psychotomimetic Dosages and Formulations" (Published September 10, 2020) From **Paragraph [0082]** "For the purpose of this disclosure, the present inventors define "neuroplastogen dose" and in particular "neuroplastogen dose of drugs classified as **5-HT2A agonists**", as a dose, dosage, posology or formulation, including **modified release** formulations, of a substance with 5-HT2A agonist actions and actions on neural plasticity, including modulation of NMDARs, that is well tolerated, safe, when administered at doses, dosages, posology and or formulations, that does not cause clinically meaningful psychedelic/psychotomimetic effects." From **Claim 1** "A compound comprising a structural analogue to **psilocin**, norpsilocin, **psilocybin**, baeocystin, norbaeocystin or **N,N-dimethyltryptamine**, according to formula I…" From **Claim 2** "A compound comprising a structural analogue to **2,5-Dimethoxy-4-iodoamphetamine**, according to formula II…" From **Claim 3** "A compound comprising a structural analogue to **Lysergic acid diethylamide**, according to formula III…" From **Claim 4** "A compound comprising a structural analogue to **ibogaine**, according to formula IV…" 7. Int'l Pat. App. Pub. No. WO/2022/212854 "Methods and Compositions Relating to Psychedelics and Serotonin Receptor Modulators" (Published November 6, 2022)\ From **Claim 4** "The composition of claim 1, wherein the **psychedelic** is selected from psilocybin, psilocin, baeocystin,

	norbaeocystin, lisurgide, LSD, dimethyltryptamine, carboxamindotryptamine, ibogaine, tabemanthalog, 3,4-methylenedioxy-methamphetamine (MDMA), 1-acetyl LSD, O-acetyl psilocin, mescaline (3,4,5-trimethoxy phenethylamine), proscaline (2-(3,5-dimethoxy-4-propoxyphenyl)ethanamine), metaescaline (2-(3 -ethoxy-4, 5-dimethoxyphenyl)ethanamine), allylescaline (4-Allyloxy-3,5-dimethyloxy phenylethylamine), methallylescaline (4-Methallyloxy-3,5 dimethoxyphenethylamine), and asymbescaline (3,4-Diethoxy-5-methoxyphenethylamine), or a pharmaceutically acceptable salt, solvate, metabolite, deuterated analogue, derivative, prodrug, or combinations thereof." From **Paragraph [00376]** "In some embodiments, the compositions described herein are administered **orally**, **intravenously**, subcutaneously, by inhalation, or by an **injection**. In some embodiments, the compositions described herein are administered orally. In some embodiments, the compositions described herein are administered orally via a pill, ampoule, vial, or tablet." From **Paragraph [00377]** "As used herein, the term "**modified release**" coating encompasses coatings that delay release, sustain release, **extended release**, prevent release, minimize release and/or otherwise prolong the release of a drug relative to formulations lacking such coatings which release a drug relatively quickly (i.e., "immediate release" compositions)."