IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	ATAI Life Sciences AG	Confirmation No.:
Serial No.:	17/941,648	Group No.:
Filing or 371(c) Date:	09 September 2022	Examiner:

Entitled: IBOGAINE COMBINATION TREATMENT

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. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000)
2. Int'l Pat. Doc. No. WO/2001/052851 "METHODS FOR THE TREATMENT OF SUBSTANCE ABUSE" (Published 26 July 2001)
3. Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS" (Filed 3 August 2021)
4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687.
5. PAUL (2019) "Introduction to Basics of Pharmacology and Toxicology" *Springer*. pages 81-89.
6. HENSTRA (2017) "Toxicokinetics of ibogaine and noribogaine in a patient with prolonged multiple cardiac arrhythmias after ingestion of internet purchased ibogaine" *Clinical Toxicology*. 55(6):600-602.

Attached hereto is a claim chart providing a concise description of the relevance of each reference in the document list to the elements of the presently pending claims.

U.S.S.N. 17/941,648 Pending Claims	References
1. A method of increasing and prolonging exposure to ibogaine in a patient, while reducing exposure to noribogaine and associated risk of QT prolongation comprising administering to the patient: **(a) a drug that inhibits the metabolism of ibogaine; and** **(b) an effective amount of ibogaine, or a pharmaceutically acceptable salt thereof.**	*From the application of interest, 17/941,648, paragraph [0003] "Following oral administration,* ***ibogaine is rapidly metabolized by CYP2D6*** *in the gut wall and liver (Koenig and Hilber, 2015)* ***to its primary metabolite, noribogaine****."* 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000) From **claim 1** "A method of **administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or a pharmaceutically acceptable salt thereof, **in combination with a CYP2D6 inhibitor,** or a pharmaceutically acceptable salt thereof, **to a human in need of the intended pharmaceutical activity of such drug**, wherein said drug and said CYP2D6 inhibitor are not the same compound." From **claim 4** "**A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or pharmaceutically acceptable salt thereof, **is selected from the group consisting of** mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, **ibogaine**, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." *From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),*

	paroxetine, *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**. **In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine. Median peak noribogaine concentrations occurred at 4 hours. Compared with placebo-pretreated subjects, paroxetine-pretreated subjects had rapid (Tmax¼1.5 hours) and substantial absorption of ibogaine**, with detectable levels out to 72 hours, and an elimination half-life of 10.2 hours." 6. HENSTRA (2017) "Toxicokinetics of ibogaine and noribogaine in a patient with prolonged multiple cardiac arrhythmias after ingestion of internet purchased ibogaine" Clinical Toxicology. 55(6):600-602. From **page 600** ""**QTc-prolongation remained present until 12 days after ingestion, several days after ibogaine plasma-levels were low, implicating clinically relevant noribogaine concentrations long after ibogaine had been cleared** from the plasma.""
2. A method of treating a condition that is treatable with ibogaine in a patient in need thereof, the method comprising administering to the patient: **(a) a drug that inhibits the metabolism of ibogaine; and** **(b) a therapeutically effective amount of ibogaine, or a pharmaceutically acceptable salt thereof.**	*From the application of interest, 17/941,648, paragraph [0003] "Following oral administration,* ***ibogaine is rapidly metabolized by CYP2D6*** *in the gut wall and liver (Koenig and Hilber, 2015)* ***to its primary metabolite, noribogaine****."* 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000) From **claim 1** "A method of **administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or a pharmaceutically acceptable salt thereof, **in combination with a CYP2D6 inhibitor,** or a pharmaceutically acceptable salt thereof, **to a human in need of the intended pharmaceutical activity of such drug**, wherein said drug and said CYP2D6 inhibitor are not the same compound."

	From **claim 4** "**A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or pharmaceutically acceptable salt thereof, **is selected from the group consisting of** mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, **ibogaine**, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." From **page 8, paragraph 3** "This invention also relates to a pharmaceutical composition comprising: (a) a **therapeutically effective amount of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation** (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof; (b) an amount of a CYP2D6 inhibitor, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition for which the Therapeutic Drug referred to in (a) is intended to treat; and (c) a pharmaceutically acceptable carrier; wherein said drug and said CYP2D6 inhibitor are not the same compound." From **page 10, paragraph 6** "The term **"treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition** to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above."
3. The method of claim 2, wherein the condition is alcoholism, substance abuse disorder, or opioid use disorder.	*From the application of interest, 17/941,648, claim 7 "The method of claim 6, wherein the CYP2D6 inhibitor is abiraterone, amiodarone,* ***bupropion****, celecoxib, chloroquine, chlorpromazine, cimetidine, cinacalcet, citalopram, clobazam, clozapine, cobicistat, desvenlafaxine, diltiazem, diphenhydramine, doxorubicin, duloxetine, Echinacea, escitalopram, febuxostat,* ***fluoxetine****, fluphenazine, Gingko biloba, fluvoxamine, gefitinib, haloperidol, hydralazine, hydroxychloroquine, imatinib, labetalol, lansoprazole, lorcaserin, metoclopramide, methadone, mirabegron, olanzapine, Panax ginseng, paroxetine, pazopanib, perhexiline,*

	propafenone, progesterone, propoxyphene, quinidine, ranitidine, risperidone, ritonavir, sertraline, telithromycin, terbinafine, terfenadine, testosterone, thioridazine, trifluperidol, verapamil, or vemurafenib." 2. Int'l Pat. Doc. No. WO/2001/052851 "METHODS FOR THE TREATMENT OF SUBSTANCE ABUSE" (Published 26 July 2001) From **claim 1** "A method of **treating substance addiction** in a subject in need thereof, **which method comprises administering to said subject** a combination of: (i) a μ-opioid receptor antagonist (μORA); (ii) a calcium channel blocker (CCB) which is long-acting or in sustained-release form, or which is nimodipine in rapid release form; and (iii) **an NMDA glutamate receptor modulator.**" From **claim 4** "**A method according to claim 1 wherein the NMDA glutamate receptor modulator is** selected from the group consisting of: CCP, dizocilpine, HA966, **ibogaine**, memantine,' ifenprodil, eliprodil and acamprosate." From **claim 31** "A method according to claim 1 wherein the substance of addiction is nicotine **and the combination further comprises** at least one of a ganglion nicotinic receptor antagonist, such as mecamylamine; or a nicotinic cholinergic receptor antagonist, such as **bupropion**; or γ-vinylGABA (vigabactin) or a κ-opioid agonist." 3. Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS" (Filed 3 August 2021) From **claim 1** "A trasndermal and/or topical **pharmaceutical composition comprising**: at least one active agent selected from the group consisting of...**ibogaine**..." From **claim 19** "The **pharmaceutical composition of any one of claims 1 to 18 further comprising** at least one additional active agent selected from the group consisting of...**fluoxetine**..." From **claim 28** "**The pharmaceutical composition of any one of claims 1 to 27 indicated for the treatment and/or prevention and/or control of** chronic pain, multiple sclerosis, severe depression (treatment resistant), maor depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, **opioid addiction**, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient."

4. The method of claim 3, wherein the condition is opioid use disorder.	*From the application of interest, 17/941,648, claim 7 "The method of claim 6, wherein the CYP2D6 inhibitor is abiraterone, amiodarone, **bupropion**, celecoxib, chloroquine, chlorpromazine, cimetidine, cinacalcet, citalopram, clobazam, clozapine, cobicistat, desvenlafaxine, diltiazem, diphenhydramine, doxorubicin, duloxetine, Echinacea, escitalopram, febuxostat, **fluoxetine**, fluphenazine, Gingko biloba, fluvoxamine, gefitinib, haloperidol, hydralazine, hydroxychloroquine, imatinib, labetalol, lansoprazole, lorcaserin, metoclopramide, methadone, mirabegron, olanzapine, Panax ginseng, paroxetine, pazopanib, perhexiline, propafenone, progesterone, propoxyphene, quinidine, ranitidine, risperidone, ritonavir, sertraline, telithromycin, terbinafine, terfenadine, testosterone, thioridazine, trifluperidol, verapamil, or vemurafenib."* 3. Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS" (Filed 3 August 2021) From **claim 1** "A trasndermal and/or topical **pharmaceutical composition comprising**: at least one active agent selected from the group consisting of...**ibogaine**..." From **claim 19** "The **pharmaceutical composition of any one of claims 1 to 18 further comprising** at least one additional active agent selected from the group consisting of...**fluoxetine**..." From **claim 28** "**The pharmaceutical composition of any one of claims 1 to 27 indicated for the treatment and/or prevention and/or control of** chronic pain, multiple sclerosis, severe depression (treatment resistant), maor depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, **opioid addiction**, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient."
5. The method of claim 4, wherein a daily dose of about 20 mg of ibogaine, or a pharmaceutically acceptable salt thereof is administered to the patient.	*From the application of interest, 17/941,648, claim 7 "The method of claim 6, wherein the CYP2D6 inhibitor is abiraterone, amiodarone, **bupropion**, celecoxib, chloroquine, chlorpromazine, cimetidine, cinacalcet, citalopram, clobazam, clozapine, cobicistat, desvenlafaxine, diltiazem, diphenhydramine, doxorubicin, duloxetine, Echinacea, escitalopram, febuxostat, **fluoxetine**, fluphenazine, Gingko biloba, fluvoxamine, gefitinib, haloperidol, hydralazine, hydroxychloroquine, imatinib, labetalol, lansoprazole, lorcaserin, metoclopramide, methadone, mirabegron, olanzapine, Panax ginseng, paroxetine, pazopanib, perhexiline, propafenone, progesterone, propoxyphene, quinidine, ranitidine, risperidone, ritonavir, sertraline, telithromycin, terbinafine, terfenadine, testosterone, thioridazine, trifluperidol, verapamil, or vemurafenib."*

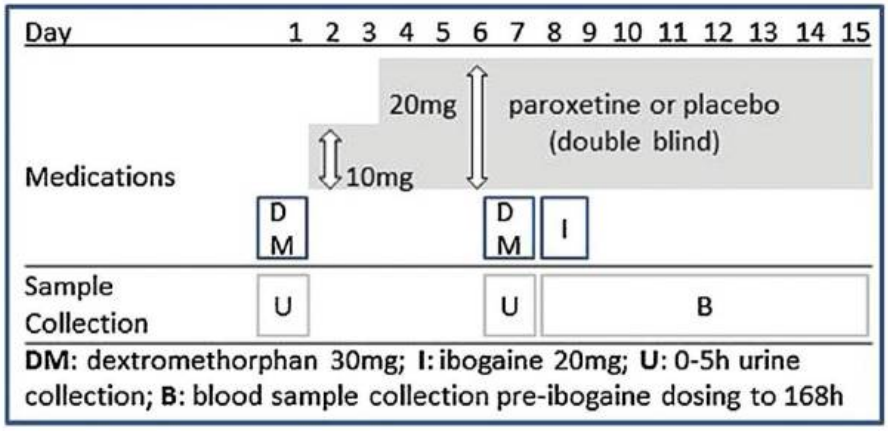
	3. Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS" (Filed 3 August 2021) From **claim 1** "A trasndermal and/or topical **pharmaceutical composition comprising**: at least one active agent selected from the group consisting of...**ibogaine**..." From **claim 3** "**A pharmaceutical composition of any one of claims 1 and 2 wherein the pharmaceutical formulation provides a dose of active agent to a patient equal to** or greater than...**10mg/day, or 25 mg/day**." From **claim 19** "The **pharmaceutical composition of any one of claims 1 to 18 further comprising** at least one additional active agent selected from the group consisting of...**fluoxetine**..." From **claim 28** "**The pharmaceutical composition of any one of claims 1 to 27 indicated for the treatment and/or prevention and/or control of** chronic pain, multiple sclerosis, severe depression (treatment resistant), maor depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, quitting smoking, alcohol addiction, cocaine addiction, **opioid addiction**, anxiety (stress), adult ADHD, cluster headaches, and cancer related or other end-of-life psychological distress in a patient."
6. The method of claim 1, wherein the drug that inhibits the metabolism of ibogaine is a CYP2D6 inhibitor.	1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000) From **claim 1** "A method of **administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or a pharmaceutically acceptable salt thereof, **in combination with a CYP2D6 inhibitor,** or a pharmaceutically acceptable salt thereof, **to a human in need of the intended pharmaceutical activity of such drug**, wherein said drug and said CYP2D6 inhibitor are not the same compound." From **claim 4** "**A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or pharmaceutically acceptable salt thereof, **is selected from the group consisting of** mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, **ibogaine**, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol,

	hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." From **page 8, paragraph 3** "This invention also relates to a pharmaceutical composition comprising: (a) a **therapeutically effective amount of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation** (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof; (b) **an amount of a CYP2D6 inhibitor**, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition for which the Therapeutic Drug referred to in (a) is intended to treat; and (c) a pharmaceutically acceptable carrier; wherein said drug and said CYP2D6 inhibitor are not the same compound." From **page 10, paragraph 6** "The term **"treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition** to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above."
7. The method of claim 6, wherein the CYP2D6 inhibitor is abiraterone, amiodarone, bupropion, celecoxib, chloroquine, chlorpromazine, cimetidine, cinacalcet, citalopram, clobazam, clozapine, cobicistat, desvenlafaxine, diltiazem, diphenhydramine, doxorubicin, duloxetine, Echinacea, escitalopram, febuxostat, fluoxetine, fluphenazine, Gingko biloba, fluvoxamine,	1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000) From **claim 1** "A method of **administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or a pharmaceutically acceptable salt thereof, **in combination with a CYP2D6 inhibitor,** or a pharmaceutically acceptable salt thereof, **to a human in need of the intended pharmaceutical activity of such drug**, wherein said drug and said CYP2D6 inhibitor are not the same compound." From **claim 4** "**A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or pharmaceutically acceptable salt thereof, **is selected from the group consisting of** mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, **ibogaine**, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram,

gefitinib, haloperidol, hydralazine, hydroxychloroquine, imatinib, labetalol, lansoprazole, lorcaserin, metoclopramide, methadone, mirabegron, olanzapine, Panax ginseng, paroxetine, pazopanib, perhexiline, propafenone, progesterone, propoxyphene, quinidine, ranitidine, risperidone, ritonavir, sertraline, telithromycin, terbinafine, terfenadine, testosterone, thioridazine, trifluperidol, verapamil, or vemurafenib.	dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." From **claim 5** "A method according to claim 1, wherein the **CYP2D6 inhibito**r, or pharmaceutically acceptable salt thereof, **is selected from** the group consisting of **quinidine**, ajmalacine, **sertraline**, venlafaxine, dexmedetomidine, tripennelamine, premethazine, hydroxyzine, halofrintane, **chloroquine**, moclobemide, and pharmaceutically acceptable salts thereof, and St. John's wort, or an extract or component thereof." From **page 8, paragraph 3** "This invention also relates to a pharmaceutical composition comprising: (a) a **therapeutically effective amount of a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation** (also referred to throughout this document as a "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof; (b) **an amount of a CYP2D6 inhibitor**, or a pharmaceutically acceptable salt thereof, that is effective in treating the disorder or condition for which the Therapeutic Drug referred to in (a) is intended to treat; and (c) a pharmaceutically acceptable carrier; wherein said drug and said CYP2D6 inhibitor are not the same compound." From **page 10, paragraph 6** "The term **"treatment", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition** to which such term applies, or one or more symptoms of such condition or disorder. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above." 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine.**"

8. The method of claim 6, wherein the CYP2D6 inhibitor is bupropion.	2. Int'l Pat. Doc. No. WO/2001/052851 "METHODS FOR THE TREATMENT OF SUBSTANCE ABUSE" (Published 26 July 2001) From **claim 1** "A method of **treating substance addiction** in a subject in need thereof, which method comprises administering to said subject a combination of: (i) a μ-opioid receptor antagonist (μORA); (ii) a calcium channel blocker (CCB) which is long-acting or in sustained-release form, or which is nimodipine in rapid release form; and (iii) **an NMDA glutamate receptor modulator**." From **claim 4** "**A method according to claim 1 wherein the NMDA glutamate receptor modulator is** selected from the group consisting of: CCP, dizocilpine, HA966, **ibogaine**, memantine,' ifenprodil, eliprodil and acamprosate." From **claim 31** "A method according to claim 1 wherein the substance of addiction is nicotine **and the combination further comprises** at least one of a ganglion nicotinic receptor antagonist, such as mecamylamine; or a nicotinic cholinergic receptor antagonist, such as **bupropion**; or γ-vinylGABA (vigabactin) or a κ-opioid agonist."
9. T he method of claim 6, wherein the CYP2D6 inhibitor is fluoxetine.	3. Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS" (Filed 3 August 2021) From **claim 1** "A trasndermal and/or topical **pharmaceutical composition comprising**: at least one active agent selected from the group consisting of...**ibogaine**..." From **claim 19** "The **pharmaceutical composition of any one of claims 1 to 18 further comprising** at least one additional active agent selected from the group consisting of...**fluoxetine**..."
10. The method of claim 6, wherein the CYP2D6 inhibitor is quinidine.	1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000) From **claim 1** "A method of **administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or a pharmaceutically acceptable salt thereof, **in combination with a CYP2D6 inhibitor,** or a pharmaceutically acceptable salt thereof, **to a human in need of the intended pharmaceutical activity of such drug**, wherein said drug and said CYP2D6 inhibitor are not the same compound." From **claim 4** "**A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or pharmaceutically acceptable salt thereof, **is**

	selected from the group consisting of mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, **ibogaine**, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." From **claim 5** "A method according to claim 1, wherein **the CYP2D6 inhibitor**, or pharmaceutically acceptable salt thereof, **is selected from the group consisting of quinidine**, ajmalacine, sertraline, venlafaxine, dexmedetomidine, tripennelamine, premethazine, hydroxyzine, halofrintane, chloroquine, moclobemide, and pharmaceutically acceptable salts thereof, and St. John's wort, or an extract or component thereof."
11. The method of claim 6, comprising administering the CYP2D6 inhibitor within about 12 hours of administration of ibogaine or a pharmaceutically acceptable salt thereof.	4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine.**" From **page 681** "**Subjects were randomized to receive** double blind **capsules containing paroxetine** or placebo between days 2 and 15 (**10 mg on days 2–3 and 20 mg/day on days 4–15**, according to a computer-generated random code). On day 7, subjects were given a single 30 mg dose of dextromethorphan, and urine was collected for the next 5 hours, for repeated CYP2D6 phenotyping. **On day 8, a single 20 mg dose of ibogaine was administered to all subjects**, and 8 mL blood samples collected pre-dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post dose." From **page 681**



1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000)

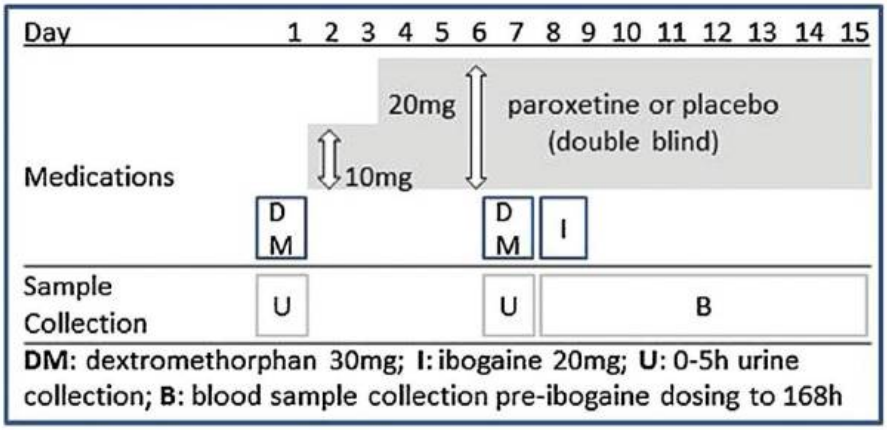
From **claim 1** "A method of **administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or a pharmaceutically acceptable salt thereof, **in combination with a CYP2D6 inhibitor,** or a pharmaceutically acceptable salt thereof, **to a human in need of the intended pharmaceutical activity of such drug**, wherein said drug and said CYP2D6 inhibitor are not the same compound."

From **claim 4** "**A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or pharmaceutically acceptable salt thereof, **is selected from the group consisting of** mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, **ibogaine**, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof."

From **page 13, paragraph 2** "Method: 1. **Subjects** that are predetermined to be extensive metabolizers (EMs; those individuals with functional CYP2D6 activity) **are administered an oral dose of a compound being tested as a**

	CYP2D6 inhibitor. 2. **Concomitantly**, or at some predetermined time period after the dose of the CYP2D6 inhibitor, **these subjects are administered a dose of a drug known to be primarily cleared via CYP2D6 mediated metabolism.**"
12. The method of claim 6, comprising administering the CYP2D6 inhibitor with the ibogaine or a pharmaceutically acceptable salt thereof.	1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS IN COMBINATION THERAPIES" (Published 12 October 2000) From **claim 1** "A method of **administering a drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or a pharmaceutically acceptable salt thereof, **in combination with a CYP2D6 inhibitor,** or a pharmaceutically acceptable salt thereof, **to a human in need of the intended pharmaceutical activity of such drug**, wherein said drug and said CYP2D6 inhibitor are not the same compound." From **claim 4** "**A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated oxidative biotransformation,** or pharmaceutically acceptable salt thereof, **is selected from the group consisting of** mequitazine, tamsulosin, oxybutynin, ritonavir, iloperidone, **ibogaine**, delavirdine, tolteridine, promethazine, pimozide, epinastine, tramodol, procainamide, methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol, amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine, clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram, dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide, ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol, hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine, methoxyphenamine, methylenedioxymethamphetamine, metoprolol, mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline, perphenazine, phenformine, promethazine, propafenone, propanolol, risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron, venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." From **page 13, paragraph 2** "Method: 1. **Subjects** that are predetermined to be extensive metabolizers (EMs; those individuals with functional CYP2D6 activity) **are administered an oral dose of a compound being tested as a CYP2D6 inhibitor.** 2. **Concomitantly**, or at some predetermined time period after the dose of the CYP2D6 inhibitor, **these subjects are administered a dose of a drug known to be primarily cleared via CYP2D6 mediated metabolism.**"
13. The method of claim 1, wherein the drug that inhibits the metabolism of	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),*

ibogaine is a CYP2D6 inactivator.	***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**"
14. The method of claim 13, wherein the CYP2D6 inactivator is 3,4-methylenedioxymethamphetamine (MDMA), paroxetine, cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone.	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**"
15. The method of claim 13, comprising administering the CYP2D6 inactivator at least 1 day prior to administration of the ibogaine or a pharmaceutically acceptable salt thereof.	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokineticprofiles of both analytes after **a single oral 20 mg dose of**

	ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine"
16. The method of claim 13, comprising co-administering the CYP2D6 inactivator with the ibogaine or a pharmaceutically acceptable salt thereof.	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine.**" From **page 681** "**Subjects were randomized to receive** double blind **capsules containing paroxetine** or placebo between days 2 and 15 (**10 mg on days 2–3 and 20 mg/day on days 4–15**, according to a computer-generated random code). On day 7, subjects were given a single 30 mg dose of dextromethorphan, and urine was collected for the next 5 hours, for repeated CYP2D6 phenotyping. **On day 8, a single 20 mg dose of ibogaine was administered to all subjects**, and 8 mL blood samples collected pre-dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post dose." From **page 681** 
17. The method of claim 1, comprising pre-treating the	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from***

patient with the drug that inhibits ibogaine metabolism prior to administration of the ibogaine or a pharmaceutically acceptable salt thereof.	*the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**"
18. The method of claim 17, comprising pre-treating the patient with the drug that inhibits ibogaine metabolism for at least 3 days prior to administration of the ibogaine or a pharmaceutically acceptable salt thereof.	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**"
19. The method of claim 17, comprising pre-treating the patient with the drug that inhibits ibogaine metabolism for about 5 days prior to administration of the ibogaine or a pharmaceutically acceptable salt thereof.	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours

	pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**"
20. The method of claim 1, wherein the administration of the drug that inhibits the metabolism of ibogaine reduces the patient's systemic exposure to noribogaine compared to a patient administered an effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**" From **page 686** "In **placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine, with undetectable ibogaine levels in all subjects by 4 hours post dose**. Median peak noribogaine concentrations occurred by 4 hours. Compared with placebo-pretreated subjects, **subjects who had reduced CYP2D6 activity from paroxetine pretreatment had rapid (median Tmax¼1.5 hours) and substantial absorption of ibogaine, with detectable levels out to72 hours**, and an elimination half-life of 10.2 hours." From **page 684** **Table 1.** Influence of Placebo or Paroxetine Pretreatment on Mean (SD) Plasma Ibogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Moiety AUC_{0-t} Following a Single 20 mg Oral Dose of Ibogaine Pretreatment Analyte | Parameter | Placebo (n = 9) | Paroxetine (n = 11) | P Ibogaine | AUC_{0-t} (ng · h/mL) | 3.6 (7.2) | 238.2 (202.1) | .0028 C_{max} (ng/mL) | 1.1 (1.8) | 29.5 (16.8) | <.0001 T_{max} (hours)* | 1.0 (0–3) | 1.5 (0–3) | .17 $t_{1/2}$ (hours) | 2.5 (0.9) | 10.2 (7.8) | .009 Noribogaine | AUC_{0-t} (ng · h/mL) | 277.4 (116.9) | 304.1 (127.9) | .64 C_{max} (ng/mL) | 18.7 (7.3) | 12.7 (5.3) | .05 T_{max} (hours)* | 4.0 (2–4) | 3.0 (1.5–8) | .63 $t_{1/2}$ (hours) | 13.0 (4.7) | 20.1 (10.2) | .07 Active moiety | AUC_{0-t} (nM · h/mL) | 948 (407) | 1793 (695) | .005 *Median (range).
21. The method of claim 1, wherein the administration of the drug that inhibits the	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),*

metabolism of ibogaine reduces the patient's noribogaine C max compared to a patient administered an effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.	***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**" From **page 682** "Although mean **noribogaine** AUC0–t values were similar in both groups, mean **Cmax was lower (12.7 vs. 18.7 ng/mL;P¼.05) and t1/2 longer (20.1 vs. 13.0 hours;P¼.07) in paroxetine-pretreated compared with placebo-pretreated subjects** (Table 1)." From **page 684** **Table 1.** Influence of Placebo or Paroxetine Pretreatment on Mean (SD) Plasma Ibogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Moiety AUC_{0-t} Following a Single 20 mg Oral Dose of Ibogaine Pretreatment Analyte / Parameter / Placebo (n = 9) / Paroxetine (n = 11) / P Ibogaine / AUC_{0-t} (ng · h/mL) / 3.6 (7.2) / 238.2 (202.1) / .0028 / C_{max} (ng/mL) / 1.1 (1.8) / 29.5 (16.8) / <.0001 / T_{max} (hours)* / 1.0 (0–3) / 1.5 (0–3) / .17 / $t_{1/2}$ (hours) / 2.5 (0.9) / 10.2 (7.8) / .009 Noribogaine / AUC_{0-t} (ng · h/mL) / 277.4 (116.9) / 304.1 (127.9) / .64 / C_{max} (ng/mL) / 18.7 (7.3) / 12.7 (5.3) / .05 / T_{max} (hours)* / 4.0 (2–4) / 3.0 (1.5–8) / .63 / $t_{1/2}$ (hours) / 13.0 (4.7) / 20.1 (10.2) / .07 Active moiety / AUC_{0-t} (nM · h/mL) / 948 (407) / 1793 (695) / .005 *Median (range).
22. A method of increasing the bioavailability of ibogaine in a patient in need thereof comprising administering to the patient: **(a) a drug that inhibits the metabolism of ibogaine; and (b) an effective amount of ibogaine, or a pharmaceutically acceptable salt thereof.**	4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine.** In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine. Median peak noribogaine concentrations occurred at 4 hours. **Compared with placebo-pretreated subjects, paroxetine-pretreated subjects had rapid (Tmax¼1.5 hours) and substantial absorption of ibogaine**, with detectable levels out to 72 hours, and an elimination half-life of 10.2 hours."

	5. PAUL (2019) "Introduction to Basics of Pharmacology and Toxicology" Springer. pages 81-89. From **page 81** "**Drug absorption is quantified in terms of bioavailability. Bioavailability is the extent to which absorption occurs**. In other words, bioavailability is the fraction of the administered drug that reaches the systemic circulation in the unchanged form."
23. The method of claim 21, wherein the patient's noribogaine C max is reduced by about 5% to about 30% compared to the patient administered the effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**" From **page 682** "Although mean **noribogaine** AUC0–t values were similar in both groups, mean **Cmax was lower (12.7 vs. 18.7 ng/mL;P¼.05) and t1/2 longer (20.1 vs. 13.0 hours;P¼.07) in paroxetine-pretreated compared with placebo-pretreated subjects** (Table 1)." From **page 684** **Table 1.** Influence of Placebo or Paroxetine Pretreatment on Mean (SD) Plasma Ibogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Moiety AUC_{0-t}, Following a Single 20 mg Oral Dose of Ibogaine Pretreatment Analyte / Parameter / Placebo (n = 9) / Paroxetine (n = 11) / P Ibogaine / AUC_{0-t} (ng · h/mL) / 3.6 (7.2) / 238.2 (202.1) / .0028 / C_{max} (ng/mL) / 1.1 (1.8) / 29.5 (16.8) / <.0001 / T_{max} (hours)[a] / 1.0 (0–3) / 1.5 (0–3) / .17 / $t_{1/2}$ (hours) / 2.5 (0.9) / 10.2 (7.8) / .009 Noribogaine / AUC_{0-t} (ng · h/mL) / 277.4 (116.9) / 304.1 (127.9) / .64 / C_{max} (ng/mL) / 18.7 (7.3) / 12.7 (5.3) / .05 / T_{max} (hours)[a] / 4.0 (2–4) / 3.0 (1.5–8) / .63 / $t_{1/2}$ (hours) / 13.0 (4.7) / 20.1 (10.2) / .07 Active moiety / AUC_{0-t} (nM · h/mL) / 948 (407) / 1793 (695) / .005 [a]Median (range).
24. The method of claim 1, wherein the administration of the drug that inhibits the	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),*

metabolism of ibogaine increases the patient's ibogaine C max compared to a patient administered an effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.	***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**" From **page 686** "In **placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine, with undetectable ibogaine levels in all subjects by 4 hours post dose**. Median peak noribogaine concentrations occurred by 4 hours. Compared with placebo-pretreated subjects, **subjects who had reduced CYP2D6 activity from paroxetine pretreatment had rapid (median Tmax¼1.5 hours) and substantial absorption of ibogaine, with detectable levels out to72 hours**, and an elimination half-life of 10.2 hours." From **page 684** **Table 1.** Influence of Placebo or Paroxetine Pretreatment on Mean (SD) Plasma Ibogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Moiety AUC_{0-t} Following a Single 20 mg Oral Dose of Ibogaine Pretreatment Analyte / Parameter / Placebo (n = 9) / Paroxetine (n = 11) / P Ibogaine / AUC_{0-t} (ng · h/mL) / 3.6 (7.2) / 238.2 (202.1) / .0028 C_{max} (ng/mL) / 1.1 (1.8) / 29.5 (16.8) / <.0001 T_{max} (hours)[a] / 1.0 (0–3) / 1.5 (0–3) / .17 $t_{1/2}$ (hours) / 2.5 (0.9) / 10.2 (7.8) / .009 Noribogaine / AUC_{0-t} (ng · h/mL) / 277.4 (116.9) / 304.1 (127.9) / .64 C_{max} (ng/mL) / 18.7 (7.3) / 12.7 (5.3) / .05 T_{max} (hours)[a] / 4.0 (2–4) / 3.0 (1.5–8) / .63 $t_{1/2}$ (hours) / 13.0 (4.7) / 20.1 (10.2) / .07 Active moiety / AUC_{0-t} (nM · h/mL) / 948 (407) / 1793 (695) / .005 [a]Median (range).
25. The method of claim 24, wherein the patient's ibogaine C max is increased by about 5% to about 30% compared to a patient administered the effective amount of ibogaine without administration of the drug that inhibits the	*From the application of interest, 17/941,648, paragraph [0010] "In some embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6 inactivator. In some embodiments,* ***the CYP2D6 inactivator is selected from*** *the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),* ***paroxetine,*** *cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."* 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687.

metabolism of ibogaine.	From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine**" From **page 686** "In **placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine, with undetectable ibogaine levels in all subjects by 4 hours post dose**. Median peak noribogaine concentrations occurred by 4 hours. Compared with placebo-pretreated subjects, **subjects who had reduced CYP2D6 activity from paroxetine pretreatment had rapid (median Tmax¼1.5 hours) and substantial absorption of ibogaine, with detectable levels out to72 hours**, and an elimination half-life of 10.2 hours." From **page 684** **Table 1.** Influence of Placebo or Paroxetine Pretreatment on Mean (SD) Plasma Ibogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Moiety AUC_{0-t} Following a Single 20 mg Oral Dose of Ibogaine Pretreatment Analyte | Parameter | Placebo (n = 9) | Paroxetine (n = 11) | P Ibogaine | AUC_{0-t} (ng · h/mL) | 3.6 (7.2) | 238.2 (202.1) | .0028 | C_{max} (ng/mL) | 1.1 (1.8) | 29.5 (16.8) | <.0001 | T_{max} (hours)[a] | 1.0 (0–3) | 1.5 (0–3) | .17 | $t_{1/2}$ (hours) | 2.5 (0.9) | 10.2 (7.8) | .009 Noribogaine | AUC_{0-t} (ng · h/mL) | 277.4 (116.9) | 304.1 (127.9) | .64 | C_{max} (ng/mL) | 18.7 (7.3) | 12.7 (5.3) | .05 | T_{max} (hours)[a] | 4.0 (2–4) | 3.0 (1.5–8) | .63 | $t_{1/2}$ (hours) | 13.0 (4.7) | 20.1 (10.2) | .07 Active moiety | AUC_{0-t} (nM · h/mL) | 948 (407) | 1793 (695) | .005 [a]Median (range).
26. The method of claim 1, wherein the effective amount of ibogaine administered in combination with a drug that inhibits the metabolism is lower than an effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.	4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine. In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine. Median peak noribogaine concentrations occurred at 4 hours. Compared with placebo-pretreated subjects, paroxetine-pretreated subjects had rapid (Tmax¼1.5 hours) and substantial absorption of ibogaine**, with detectable levels out to 72 hours, and an elimination half-life of 10.2 hours." From **page 684**

	Table 1. Influence of Placebo or Paroxetine Pretreatment on Mean (SD) Plasma Ibogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Moiety AUC_{0-t} Following a Single 20 mg Oral Dose of Ibogaine Pretreatment Analyte / Parameter / Placebo (n = 9) / Paroxetine (n = 11) / P Ibogaine: AUC_{0-t} (ng · h/mL) 3.6 (7.2) 238.2 (202.1) .0028 C_{max} (ng/mL) 1.1 (1.8) 29.5 (16.8) <.0001 T_{max} (hours)* 1.0 (0–3) 1.5 (0–3) .17 $t_{1/2}$ (hours) 2.5 (0.9) 10.2 (7.8) .009 Noribogaine: AUC_{0-t} (ng · h/mL) 277.4 (116.9) 304.1 (127.9) .64 C_{max} (ng/mL) 18.7 (7.3) 12.7 (5.3) .05 T_{max} (hours)* 4.0 (2–4) 3.0 (1.5–8) .63 $t_{1/2}$ (hours) 13.0 (4.7) 20.1 (10.2) .07 Active moiety: AUC_{0-t} (nM · h/mL) 948 (407) 1793 (695) .005 *Median (range).
27. The method of claim 26, wherein the effective amount of ibogaine is about 5% to about 50% lower than an effective amount of ibogaine without administration of the drug that inhibits the metabolism of ibogaine.	4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine. In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine. Median peak noribogaine concentrations occurred at 4 hours. Compared with placebo-pretreated subjects, paroxetine-pretreated subjects had rapid (Tmax¼1.5 hours) and substantial absorption of ibogaine**, with detectable levels out to 72 hours, and an elimination half-life of 10.2 hours." From **page 684** **Table 1.** Influence of Placebo or Paroxetine Pretreatment on Mean (SD) Plasma Ibogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Moiety AUC_{0-t} Following a Single 20 mg Oral Dose of Ibogaine Pretreatment Analyte / Parameter / Placebo (n = 9) / Paroxetine (n = 11) / P Ibogaine: AUC_{0-t} (ng · h/mL) 3.6 (7.2) 238.2 (202.1) .0028 C_{max} (ng/mL) 1.1 (1.8) 29.5 (16.8) <.0001 T_{max} (hours)* 1.0 (0–3) 1.5 (0–3) .17 $t_{1/2}$ (hours) 2.5 (0.9) 10.2 (7.8) .009 Noribogaine: AUC_{0-t} (ng · h/mL) 277.4 (116.9) 304.1 (127.9) .64 C_{max} (ng/mL) 18.7 (7.3) 12.7 (5.3) .05 T_{max} (hours)* 4.0 (2–4) 3.0 (1.5–8) .63 $t_{1/2}$ (hours) 13.0 (4.7) 20.1 (10.2) .07 Active moiety: AUC_{0-t} (nM · h/mL) 948 (407) 1793 (695) .005 *Median (range).
28. The method of claim 1, wherein the effective amount of ibogaine is about 20 mg to about 1000 mg.	4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine.**"

29. The method of claim 1, wherein the effective amount of ibogaine is about 10 mg to about 40 mg.	4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687. From **page 680** "Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 hours pharmacokinetic profiles of both analytes after **a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine.**"

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First Named Inventor/Applicant Name:	Srinivas G. RAO
Customer Number:	58249
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