### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: ATAI Life Sciences AG

Serial No.: 17/941,648

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Group No.: Examiner:

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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:

- 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)
- Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS" (Filed 3 August 2021)
- 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.
- 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                                     | References   |
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| Pending Claims  | Kurunus  |
| 1. A method of<br>increasing and<br>prolonging exposure | From the application of interest, 17/941,648, paragraph [0003] "Following oral administration, <b>ibogaine is rapidly metabolized by CYP2D6</b> in the gut wall and liver (Koenig and Hilber, 2015) <b>to its primary metabolite</b> ,   |
| to ibogaine in a patient, while reducing                | noribogaine."  |
| exposure to<br>noribogaine and<br>associated risk of QT | 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS<br>IN COMBINATION THERAPIES" (Published 12 October 2000)   |
| prolongation<br>comprising<br>administering to the      | From <b>claim 1</b> "A method of <b>administering a drug for which the major</b><br><b>clearance mechanism in humans is CYP2D6 mediated oxidative</b>  |
| patient:  | biotransformation, or a pharmaceutically acceptable salt thereof, in   |
| (a) a drug that inhibits                                | combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable  |
| the metabolism of                                       | salt thereof, to a human in need of the intended pharmaceutical activity   |
| ibogaine; and   | of such drug, wherein said drug and said CYP2D6 inhibitor are not the  |
| (b) an effective  | same compound."  |
| amount of ibogaine, or                                  | 1  |
| a pharmaceutically                                      | From claim 4 "A method according to claim 1, wherein the drug for  |
| acceptable salt thereof.                                | which the major clearance mechanism in humans is CYP2D6 mediated   |
|   | oxidative biotransformation, or pharmaceutically acceptable salt thereof, is<br>selected from the group consisting of mequitazine, tamsulosin,<br>oxybutynin, ritonavir, iloperidone, ibogaine, delavirdine, tolteridine,<br>promethazine, pimozide, epinastine, tramodol, procainamide,<br>methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol,<br>amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine,<br>clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram,<br>dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide,<br>ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol,<br>hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine,<br>methoxyphenamine, methylenedioxymethamphetamine, metoprolol,<br>mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-<br>propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline,<br>perphenazine, phenformine, promethazine, propafenone, propanolol,<br>risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron,<br>venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." |
|   | From the application of interest, 17/941,648, paragraph [0010] "In some<br>embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6<br>inactivator. In some embodiments, <b>the CYP2D6 inactivator is selected from</b><br>the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),   |

|  | <ul> <li>paroxetine, cimetidine, pimozide, methamphetamine, metoclopramide or desethylamiodarone."</li> <li>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.</li> <li>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."</li> <li>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.</li> <li>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.""</li> </ul> |
|--|---|
| 2. A method of<br>treating a condition<br>that is treatable with<br>ibogaine in a patient in<br>need thereof, the<br>method comprising |   |
| administering to the<br>patient:<br>(a) a drug that inhibits   | 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS<br>IN COMBINATION THERAPIES" (Published 12 October 2000)  |
| the metabolism of<br>ibogaine; and<br>(b) a therepositionly  | From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation or a pharmacautically accortable solt thereof in  |
| (b) a therapeutically<br>effective amount of<br>ibogaine, or a<br>pharmaceutically<br>acceptable salt thereof.                         | <b>biotransformation</b> , or a pharmaceutically acceptable salt thereof, in<br><b>combination with a CYP2D6 inhibitor</b> , or a pharmaceutically acceptable<br>salt thereof, <b>to a human in need of the intended pharmaceutical activity</b><br><b>of such drug</b> , wherein said drug and said CYP2D6 inhibitor are not the<br>same compound."  |

|   | From claim 4 "A method according to claim 1, wherein the drug for  |
|---|--|
|   | <b>o i i o</b>   |
|   | which the major clearance mechanism in humans is CYP2D6 mediated<br>oxidative biotransformation, or pharmaceutically acceptable salt thereof, is<br>selected from the group consisting of mequitazine, tamsulosin,<br>oxybutynin, ritonavir, iloperidone, ibogaine, delavirdine, tolteridine,<br>promethazine, pimozide, epinastine, tramodol, procainamide,<br>methamphetamine, tamoxifen, nicergoline, fluoxetine, alprenolol,<br>amiflamine, amitriptyline, aprindine, brofaromine, buturalol, cinnarizine,<br>clomipramine, codeine, debrisoquine, desipramine, desmethylcitalopram,<br>dexfenfluramine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol,<br>hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine,<br>methoxyphenamine, methylenedioxymethamphetamine, metoprolol,<br>mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-<br>propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline,<br>perphenazine, phenformine, promethazine, propafenone, propanolol,<br>risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron,<br>venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof." |
|   | <ul> <li>From page 8, paragraph 3 "This invention also relates to a pharmaceutical composition comprising:</li> <li>(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;</li> <li>(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</li> <li>(c) a pharmaceutically acceptable carrier;</li> <li>wherein said drug and said CYP2D6 inhibitor are not the same compound."</li> </ul>   |
|   | 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<br>2, wherein the<br>condition is<br>alcoholism, substance<br>abuse disorder, or<br>opioid use disorder. | From the application of interest, 17/941,648, claim 7 "The method of claim<br>6, wherein the CYP2D6 inhibitor is abiraterone, amiodarone, <b>bupropion</b> ,<br>celecoxib, chloroquine, chlorpromazine, cimetidine, cinacalcet, citalopram,<br>clobazam, clozapine, cobicistat, desvenlafaxine, diltiazem,<br>diphenhydramine, doxorubicin, duloxetine, Echinacea, escitalopram,<br>febuxostat, <b>fluoxetine</b> , fluphenazine, Gingko biloba, fluvoxamine, gefitinib,<br>haloperidol, hydralazine, hydroxychloroquine, imatinib, labetalol,<br>lansoprazole, lorcaserin, metoclopramide, methadone, mirabegron,<br>olanzapine, Panax ginseng, paroxetine, pazopanib, perhexiline,   |

| propafenone, progesterone, propoxyphene, quinidine, ranitidine,<br>risperidone, ritonavir, sertraline, telithromycin, terbinafine, terfenadine,<br>testosterone, thioridazine, trifluperidol, verapamil, or vemurafenib."   |
|---|
| 2. Int'l Pat. Doc. No. WO/2001/052851 "METHODS FOR THE<br>TREATMENT OF SUBSTANCE ABUSE" (Published 26 July 2001)  |
| From claim 1 "A method of treating substance addiction in a subject in<br>need thereof, which method comprises administering to said subject a<br>combination of: (i) a $\mu$ -opioid receptor antagonist ( $\mu$ ORA); (ii) a calcium<br>channel blocker (CCB) which is long-acting or in sustained-release form, or<br>which is nimodipine in rapid release form; and (iii) an NMDA glutamate<br>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 <b>claim 31</b> "A method according to claim 1 wherein the substance of addiction is nicotine <b>and the combination further comprises</b> at least one of a ganglion nicotinic receptor antagonist, such as mecamylamine; or a nicotinic cholinergic receptor antagonist, such as <b>bupropion</b> ; or $\gamma$ -vinylGABA (vigabactin) or a $\kappa$ -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 <b>claim 1</b> "A trasndermal and/or topical <b>pharmaceutical composition comprising</b> : at least one active agent selected from the group consisting of <b>ibogaine</b> "  |
| 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 offluoxetine"   |
| 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   | From the application of interest, 17/941,648, claim 7 "The method of claim  |
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| 3, wherein the   | 6, wherein the CYP2D6 inhibitor is abiraterone, amiodarone, <b>bupropion</b> ,  |
| condition is opioid use  | celecoxib, chloroquine, chlorpromazine, cimetidine, cinacalcet, citalopram,   |
| disorder.  | clobazam, clozapine, cobicistat, desvenlafaxine, diltiazem,   |
| uisor der .  | diphenhydramine, doxorubicin, duloxetine, Echinacea, escitalopram,  |
|  | febuxostat, <b>fluoxetine</b> , 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 <b>claim 1</b> "A trasndermal and/or topical <b>pharmaceutical composition comprising</b> : at least one active agent selected from the group consisting of <b>ibogaine</b> "  |
|  | 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 offluoxetine"   |
|  | From claim 28 "The pharmaceutical composition of any one of claims 1<br>to 27 indicated for the treatment and/or prevention and/or control of<br>chronic pain, multiple sclerosis, severe depression (treatment resistant),<br>maor depressive disorder, obsessive-compulsive disorder, post-traumatic<br>stress disorder, quitting smoking, alcohol addiction, cocaine addiction,<br>opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and<br>cancer related or other end-of-life psychological distress in a patient." |
| 5. The method of claim<br>4, wherein a daily dose<br>of about 20 mg of | From the application of interest, 17/941,648, claim 7 "The method of claim 6, wherein the CYP2D6 inhibitor is abiraterone, amiodarone, <b>bupropion</b> , celecoxib, chloroquine, chlorpromazine, cimetidine, cinacalcet, citalopram,   |
| ibogaine, or a   | clobazam, clozapine, cobicistat, desvenlafaxine, diltiazem,   |
| pharmaceutically   | diphenhydramine, doxorubicin, duloxetine, Echinacea, escitalopram,  |
| acceptable salt thereof  | febuxostat, <b>fluoxetine</b> , fluphenazine, Gingko biloba, fluvoxamine, gefitinib,  |
| is administered to the   | haloperidol, hydralazine, hydroxychloroquine, imatinib, labetalol,  |
| patient.   | 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."  |
|  |   |

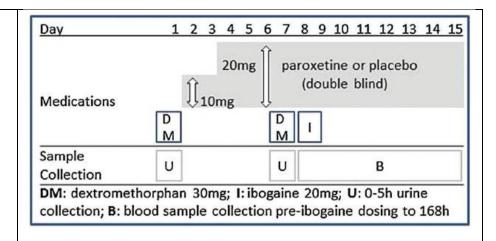
|   | 3. Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS" (Filed 3 August 2021)   |
|---|---|
|   | From <b>claim 1</b> "A trasndermal and/or topical <b>pharmaceutical composition comprising</b> : at least one active agent selected from the group consisting of <b>ibogaine</b> "  |
|   | 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 than10mg/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 offluoxetine"   |
|   | From claim 28 "The pharmaceutical composition of any one of claims 1<br>to 27 indicated for the treatment and/or prevention and/or control of<br>chronic pain, multiple sclerosis, severe depression (treatment resistant),<br>maor depressive disorder, obsessive-compulsive disorder, post-traumatic<br>stress disorder, quitting smoking, alcohol addiction, cocaine addiction,<br>opioid addiction, anxiety (stress), adult ADHD, cluster headaches, and<br>cancer related or other end-of-life psychological distress in a patient." |
| 6. The method of claim<br>1, wherein the drug | 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS<br>IN COMBINATION THERAPIES" (Published 12 October 2000)  |
| that inhibits the                             |   |
| metabolism of                                 | From claim 1 "A method of administering a drug for which the major  |
| ibogaine is a CYP2D6                          | clearance mechanism in humans is CYP2D6 mediated oxidative  |
| inhibitor.                                    | biotransformation, or a pharmaceutically acceptable salt thereof, in  |
|   | combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable   |
|   | salt thereof, <b>to a human in need of the intended pharmaceutical activity</b><br><b>of such drug</b> , 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<br>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, <b>ibogaine</b> , delavirdine, tolteridine,   |
|   | promethazine, pimozide, epinastine, tramodol, procainamide,<br>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,   |

|   | propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline,  |
|---|---|
|   | perphenazine, phenformine, promethazine, propafenone, propanolol,   |
|   | risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron,   |
|   | venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof."  |
|   | From <b>page 8</b> , <b>paragraph 3</b> "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   | 1 Int'l Pat Doc. No. WO/2000/059486 "USE OF CVP2D6 INHIBITORS   |
| 7. The method of claim<br>6. wherein the  | 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS<br>IN COMBINATION THERAPIES" (Published 12 October 2000)  |
| 6, wherein the  | 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS         IN COMBINATION THERAPIES" (Published 12 October 2000)   |
|   |   |
| 6, wherein the<br>CYP2D6 inhibitor is   | IN COMBINATION THERAPIES" (Published 12 October 2000)   |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,   | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in   |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,   | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable  |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,  | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable<br>salt thereof, to a human in need of the intended pharmaceutical activity  |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,   | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable<br>salt thereof, to a human in need of the intended pharmaceutical activity<br>of such drug, wherein said drug and said CYP2D6 inhibitor are not the   |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,  | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable<br>salt thereof, to a human in need of the intended pharmaceutical activity  |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,  | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable<br>salt thereof, to a human in need of the intended pharmaceutical activity<br>of such drug, wherein said drug and said CYP2D6 inhibitor are not the<br>same compound."  |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,<br>desvenlafaxine,   | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable<br>salt thereof, to a human in need of the intended pharmaceutical activity<br>of such drug, wherein said drug and said CYP2D6 inhibitor are not the<br>same compound."<br>From claim 4 "A method according to claim 1, wherein the drug for   |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,<br>desvenlafaxine,<br>diltiazem,   | <ul> <li>IN COMBINATION THERAPIES" (Published 12 October 2000)</li> <li>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."</li> <li>From claim 4 "A method according to claim 1, wherein the drug for which the major clearance mechanism in humans is CYP2D6 mediated</li> </ul>  |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,<br>desvenlafaxine,   | IN COMBINATION THERAPIES" (Published 12 October 2000)<br>From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable<br>salt thereof, to a human in need of the intended pharmaceutical activity<br>of such drug, wherein said drug and said CYP2D6 inhibitor are not the<br>same compound."<br>From claim 4 "A method according to claim 1, wherein the drug for   |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,<br>desvenlafaxine,<br>diltiazem,<br>diphenhydramine,   | <ul> <li>IN COMBINATION THERAPIES" (Published 12 October 2000)</li> <li>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."</li> <li>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</li> </ul>   |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,<br>desvenlafaxine,<br>diltiazem,<br>diltiazem,<br>diphenhydramine,<br>doxorubicin,<br>duloxetine, Echinacea,<br>escitalopram,              | <ul> <li>IN COMBINATION THERAPIES" (Published 12 October 2000)</li> <li>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."</li> <li>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,</li> </ul>  |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,<br>desvenlafaxine,<br>diltiazem,<br>diphenhydramine,<br>doxorubicin,<br>duloxetine, Echinacea,<br>escitalopram,<br>febuxostat, fluoxetine, | <ul> <li>IN COMBINATION THERAPIES" (Published 12 October 2000)</li> <li>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."</li> <li>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,</li> </ul> |
| 6, wherein the<br>CYP2D6 inhibitor is<br>abiraterone,<br>amiodarone,<br>bupropion, celecoxib,<br>chloroquine,<br>chlorpromazine,<br>cimetidine, cinacalcet,<br>citalopram, clobazam,<br>clozapine, cobicistat,<br>desvenlafaxine,<br>diltiazem,<br>diphenhydramine,<br>doxorubicin,<br>duloxetine, Echinacea,<br>escitalopram,                            | <ul> <li>IN COMBINATION THERAPIES" (Published 12 October 2000)</li> <li>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."</li> <li>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,</li> </ul>  |

| gefitinib, haloperidol, | dexfenfluramine, dextromethorphan, dihydrocodine, dolasetron, encainide,   |
|-------------------------|--|
| hydralazine,            | ethylmorphine, flecainide, flunarizine, fluvoxamine, guanoxan, haloperidol,  |
| hydroxychloroquine,     | hydrocodone, indoramin, imipramine, maprotiline, methoxyamphetamine,   |
| imatinib, labetalol,    | methoxyphenamine, methylenedioxymethamphetamine, metoprolol,   |
| lansoprazole,           | mexiletine, mianserin, minaprine, procodeine, nortriptyline, N-  |
| lorcaserin,             | propylajmaline, ondansetron, oxycodone, paroxetine, perhexiline,   |
| metoclopramide,         | perphenazine, phenformine, promethazine, propafenone, propanolol,  |
| methadone,              | risperidone, sparteine, thioridazine, timolol, tomoxetine, tropisetron,  |
| mirabegron,             | venlafaxine, zuclopenthixol, and pharmaceutically acceptable salts thereof."   |
| olanzapine, Panax       |  |
| ginseng, paroxetine,    | From <b>claim 5</b> "A method according to claim 1, wherein the <b>CYP2D6</b>  |
| pazopanib,              | inhibitor, or pharmaceutically acceptable salt thereof, is selected from the   |
| perhexiline,            | group consisting of <b>quinidine</b> , ajmalacine, <b>sertraline</b> , venlafaxine,  |
| propafenone,            | dexmedetomidine, tripennelamine, premethazine, hydroxyzine, halofrintane,  |
| progesterone,           | chloroquine, moclobemide, and pharmaceutically acceptable salts thereof,   |
| propoxyphene,           | and St. John's wort, or an extract or component thereof."  |
| quinidine, ranitidine,  |  |
| risperidone, ritonavir, | From <b>page 8</b> , <b>paragraph 3</b> "This invention also relates to a pharmaceutical   |
| sertraline,             | composition comprising:  |
| telithromycin,          | (a) a therapeutically effective amount of a drug for which the major   |
| terbinafine,            | clearance mechanism in humans is CYP2D6 mediated oxidative   |
| terfenadine,            | <b>biotransformation</b> (also referred to throughout this document as a   |
| testosterone,           | "Therapeutic Drug"), or a pharmaceutically acceptable salt thereof;  |
| thioridazine,           | (b) an amount of a CYP2D6 inhibitor, or a pharmaceutically acceptable  |
| trifluperidol,          | salt thereof, that is effective in treating the disorder or condition for which  |
| verapamil, or           | the Therapeutic Drug referred to in (a) is intended to treat; and  |
| vemurafenib.            | (c) a pharmaceutically acceptable carrier;   |
|                         | wherein said drug and said CYP2D6 inhibitor are not the same compound."  |
|                         |  |
|                         | From <b>page 10</b> , <b>paragraph 6</b> "The term <b>"treatment"</b> , <b>as used herein</b> , <b>refers to reversing</b> , <b>alleviating</b> , <b>inhibiting the progress of</b> , <b>or preventing</b> |
|                         | 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 <b>page 680</b> "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<br>ibogaine in 21 healthy subjects who had been pretreated for 6 days with<br>placebo or the CYP2D6 inhibitor paroxetine."     |
|                         |  |

| 8. The method of claim<br>6, wherein the<br>CYP2D6 inhibitor is                 | 2. Int'l Pat. Doc. No. WO/2001/052851 "METHODS FOR THE<br>TREATMENT OF SUBSTANCE ABUSE" (Published 26 July 2001)  |
|---|---|
| bupropion.  | From claim 1 "A method of treating substance addiction in a subject in<br>need thereof, which method comprises administering to said subject a<br>combination of: (i) a $\mu$ -opioid receptor antagonist ( $\mu$ ORA); (ii) a calcium<br>channel blocker (CCB) which is long-acting or in sustained-release form, or<br>which is nimodipine in rapid release form; and (iii) <b>an NMDA glutamate</b><br>receptor modulator."                            |
|   | From claim 4 "A method according to claim 1 wherein the NMDA<br>glutamate receptor modulator is selected from the group consisting of:<br>CCP, dizocilpine, HA966, ibogaine, memantine,' ifenprodil, eliprodil and<br>acamprosate."   |
|   | From <b>claim 31</b> "A method according to claim 1 wherein the substance of addiction is nicotine <b>and the combination further comprises</b> at least one of a ganglion nicotinic receptor antagonist, such as mecamylamine; or a nicotinic cholinergic receptor antagonist, such as <b>bupropion</b> ; or $\gamma$ -vinylGABA (vigabactin) or a $\kappa$ -opioid agonist."  |
| 9. T he method of<br>claim 6, wherein the<br>CYP2D6 inhibitor is<br>fluoxetine. | 3. Priority Doc. Of Int'l Pat. Doc. No. WO/2023/012691 "TRANSDERMAL<br>MICRO-DOSING DELIVERY OF PHARMACEUTICAL AGENTS"<br>(Filed 3 August 2021)   |
|   | From <b>claim 1</b> "A trasndermal and/or topical <b>pharmaceutical composition comprising</b> : at least one active agent selected from the group consisting of <b>ibogaine</b> "  |
|   | 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 offluoxetine"   |
| 10. The method of<br>claim 6, wherein the<br>CYP2D6 inhibitor is                | 1. Int'l Pat. Doc. No. WO/2000/059486 "USE OF CYP2D6 INHIBITORS<br>IN COMBINATION THERAPIES" (Published 12 October 2000)  |
| quinidine.  | From claim 1 "A method of administering a drug for which the major<br>clearance mechanism in humans is CYP2D6 mediated oxidative<br>biotransformation, or a pharmaceutically acceptable salt thereof, in<br>combination with a CYP2D6 inhibitor, or a pharmaceutically acceptable<br>salt thereof, to a human in need of the intended pharmaceutical activity<br>of such drug, wherein said drug and said CYP2D6 inhibitor are not the<br>same compound." |
|   | From claim 4 "A method according to claim 1, wherein the drug for<br>which the major clearance mechanism in humans is CYP2D6 mediated<br>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,<br>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,<br>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."                       |
|  | venturaxine, zueropentinxoi, and pharmaceuteuriy acceptable suits thereor.   |
|  | From claim 5 "A method according to claim 1, wherein the CYP2D6  |
|  | <b>inhibitor</b> , or pharmaceutically acceptable salt thereof, <b>is selected from the</b><br><b>group consisting of quinidine</b> , 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                            | 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics   |
| claim 6, comprising                          | and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy   |
| administering the<br>CYP2D6 inhibitor        | Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687.   |
| within about 12 hours                        | From <b>page 680</b> "Conversion of ibogaine to its active metabolite noribogaine  |
| of administration of                         | appears to be mediated primarily by CYP2D6. We compared 168 hours  |
| ibogaine or a                                | pharmacokinetic profiles of both analytes after a single oral 20 mg dose of  |
| pharmaceutically<br>acceptable salt thereof. | ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine."   |
| acceptable sait thereof.                     | pracebo or the CTT 2D0 minoritor 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   |
|  | <b>was administered to all subjects</b> , and 8 mL blood samples collected pre-<br>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 <b>page 681</b>   |
|  | rom half oor   |



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, Npropylajmaline, 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** 

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

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

|   | ibogaine in 21 healthy subjects who had been pretreated for 6 days with<br>placebo or the CYP2D6 inhibitor paroxetine"   |
|---|--|
| 16. The method of<br>claim 13, comprising<br>co-administering the<br>CYP2D6 inactivator<br>with the ibogaine or a<br>pharmaceutically<br>acceptable salt thereof. | From the application of interest, 17/941,648, paragraph [0010] "In some<br>embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6<br>inactivator. In some embodiments, <b>the CYP2D6 inactivator is selected from</b><br>the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),<br><b>paroxetine,</b> cimetidine, pimozide, methamphetamine, metoclopramide or<br>desethylamiodarone."  |
|   | 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics<br>and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy<br>Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687.   |
|   | From <b>page 680</b> "Conversion of ibogaine to its active metabolite noribogaine<br>appears to be mediated primarily by CYP2D6. We compared 168 hours<br>pharmacokinetic profiles of both analytes after <b>a single oral 20 mg dose of</b><br><b>ibogaine in 21 healthy subjects who had been pretreated for 6 days with</b><br><b>placebo or the CYP2D6 inhibitor paroxetine.</b> "   |
|   | From page 681 "Subjects were randomized to receive double blind<br>capsules containing paroxetine or placebo between days 2 and 15 (10 mg<br>on days 2–3 and 20 mg/day on days 4–15, according to a computer-<br>generated random code). On day 7, subjects were given a single 30 mg dose<br>of dextromethorphan, and urine was collected for the next 5 hours, for<br>repeated CYP2D6 phenotyping. On day 8, a single 20 mg dose of ibogaine<br>was administered to all subjects, and 8 mL blood samples collected pre-<br>dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168<br>hours post dose."  |
|   | From page 681  |
|   | Day       1       2       3       4       5       6       7       8       9       10       11       12       13       14       15         20mg       paroxetine or placebo<br>(double blind)       paroxetine or placebo<br>(double blind)       0 |
| 17. The method of<br>claim 1, comprising<br>pre-treating the  | From the application of interest, 17/941,648, paragraph [0010] "In some<br>embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6<br>inactivator. In some embodiments, <b>the CYP2D6 inactivator is selected from</b>  |

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

|  | ibogaine in 2   | netic profiles of both<br>21 healthy subjects<br>he CYP2D6 inhibi  | s who had been p  | 0 0  |  |
|--|---|--|---|--|--|
| 20. The method of<br>claim 1, wherein the<br>administration of the<br>drug that inhibits the<br>metabolism of<br>ibogaine reduces the<br>patient's systemic<br>exposure to | embodiments<br>inactivator. I<br>the group co   | plication of interest,<br>s, the drug that inhit<br>In some embodimen<br>nsisting of 3,4-Meth<br>cimetidine, pimozide<br>odarone."   | bits the metabolis<br>its, <b>the CYP2D6 i</b><br>hylenedioxymetha  | m of ibogaine is a (<br>nactivator is select<br>mphetamine (MDM  | CYP2D6<br>e <b>d from</b><br>IA),  |
| noribogaine compared<br>to a patient<br>administered an  | and Pharmac   | 015) "Influence of C<br>codynamics of a Sin<br>Pharmacokinetics/P  | gle 20 mg Dose o  | of Ibogaine in Healt   | hy   |
| effective amount of<br>ibogaine without<br>administration of the<br>drug that inhibits the<br>metabolism of<br>ibogaine.   | appears to be<br>pharmacokin<br><b>ibogaine in</b> 2  | 580 "Conversion of a<br>e mediated primarily<br>netic profiles of both<br>21 healthy subjects<br>he CYP2D6 inhibi  | y by CYP2D6. W<br>n analytes after <b>a</b> s<br>s who had been p   | e compared 168 ho<br>single oral 20 mg o   | urs<br>lose of   |
|  | converted to<br>subjects by<br>occurred by  | <ul> <li>586 "In placebo-preprint of noribogaine, with 4 hours post dose.</li> <li>4 hours. Compared duced CYP2D6 act</li> </ul>   | a undetectable ib<br>Median peak nori<br>with placebo-pret<br>ivity from parox  | ogaine levels in all<br>ibogaine concentrat<br>treated subjects, su<br>tetine pretreatmen  | ions<br>b <b>jects</b>   |
|  | rapid (media  | an Tmax <sup>1</sup> ⁄41.5 hour<br>able levels out to72  |   | _  | oogaine,   |
|  | rapid (media<br>with detecta<br>hours."<br>From page 6<br>Table I. Influence of   | ble levels out to72<br>584<br>Placebo or Paroxetine Pretreatment of  | hours, and an eli   | mination half-life o   | ogaine,<br>of 10.2   |
|  | rapid (media<br>with detecta<br>hours."<br>From page 6<br>Table I. Influence of   | ible levels out to72<br>584  | hours, and an eli   | Moribogaine Pharmacokinetic Param  | ogaine,<br>of 10.2   |
|  | rapid (media<br>with detecta<br>hours."<br>From page 6<br>Table I. Influence of   | ble levels out to72<br>584<br>Placebo or Paroxetine Pretreatment of  | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine  | Moribogaine Pharmacokinetic Param  | ogaine,<br>of 10.2   |
|  | rapid (media<br>with detecta<br>hours."<br>From page 6  | 584<br>Placebo or Paroxetine Pretreatment of<br>Parameter<br>AUC <sub>bet</sub> (ng · h/mL)<br>Cnas (ng/mL)<br>Tmax (hours)*   | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatme<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)  | Noribogaine Pharmacokinetic Param<br>nt.<br>238.2 (202.1)<br>25.5 (16.8)<br>1.5 (0-3)  | pogaine,           of 10.2           eters, and Mean   |
|  | rapid (media<br>with detecta<br>hours."<br>From page 6<br>Table I. Influence of<br>Active Molety AUCo.  | AUC <sub>bet</sub> (ng-h/mL)<br>C <sub>me</sub> (ng/mL)<br>T <sub>max</sub> (ng/mL)  | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Piecebo (n = 9)<br>3.6 (72)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)  | Noribogaine Pharmacokinetic Param<br>nt.<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5-6)   | P<br>eters, and Mean<br>P<br>0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63  |
|  | rapid (media<br>with detecta<br>hours."<br>From page 6<br>Table I. Influence of<br>Active Molety AUCo.<br>Analyte   | AUC <sub>D+1</sub> (gr/mL)<br>AUC <sub>D+1</sub> (gr/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)   | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatme<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>2.77.4 (116.9)<br>18.7 (7.3)   | Noribogaine Pharmacokinetic Param<br>nt.<br>238.2 (202.1)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)  | P<br>007 10.2<br>eters, and Mean<br>P<br>0028<br><_0001<br>_17<br>_009<br>_64<br>_05   |
|  | rapid (media<br>with detecta<br>hours."<br>From page 6<br>Table I. Influence of<br>Active Molety AUCo.<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).   | AUC <sub>0-c</sub> (nM·h/mL)   | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatme<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.9 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)  | Noribogaine Pharmacokinetic Param<br>nt<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-6)<br>20.1 (10.2)<br>1793 (695)  | P<br>eters, and Mean<br>P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005  |
| 21. The method of  | rapid (media<br>with detecta<br>hours."<br>From page 6<br>Table I. Influence of<br>Active Molety AUCoor<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).  | AUC <sub>0-t</sub> (nM·h/mL)   | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>187 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, part   | INoribogaine Pharmacokinetic Param<br>nt.<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>25.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>304.1 (127.9)<br>12.7 (5.3)<br>304.1 (10.2)<br>1793 (695)<br>agraph [0010] "In   | P<br>eters, and Mean<br>P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>.005<br>.005<br>.005  |
| claim 1, wherein the   | rapid (media         with detecta         hours."         From page 6         Table 1. Influence of         Active Molety AUCool         Analyte         Ibogaine         Noribogaine         Active molety         "Median (range).         From the apple         embodiments                 | AUC <sub>b-c</sub> (nM·h/mL)<br>AUC <sub>b-c</sub> (nM·h/mL)<br>Trace (hours) <sup>a</sup><br>trace (hours) <sup>b</sup><br>trace (h | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatme<br>Placebo (n = 9)<br>3.6 (72)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, part<br>bits the metabolis                               | INoribogaine Pharmacokinetic Param<br>nt.<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5-6)<br>20.1 (10.2)<br>1793 (695)<br>agraph [0010] "In<br>m of ibogaine is a (10)                                     | pogaine,           of 10.2           eters, and Mean   |
|  | rapid (media         with detecta         hours."         From page 6         Table 1. Influence of         Active Molety AUCool         Analyte         Ibogaine         Noribogaine         Active molety         *Median (range).         From the apper embodiments         inactivator. If | AUC <sub>0-t</sub> (nM·h/mL)   | hours, and an eli<br>on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatme<br>Placebo (n = 9)<br>3.6 (72)<br>1.1 (1.8)<br>1.0 (0 - 3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, part<br>bits the metabolis<br>its, <b>the CYP2D6 i</b> | Inverties         Parametric         Parametric           nt         238.2 (202.1)         295 (16.8)           1.5 (0-3)         10.2 (7.8)         304.1 (127.9)           12.7 (5.3)         3.0 (1.5-6)         20.1 (10.2)           1793 (695)         1793 (695)         1793 (695) | Pogaine,<br>of 10.2           eters, and Mean           P           .0028           <.0001           .17           .009           .64           .05           .63           .07           .005           Some           CYP2D6           ed from |

metabolism ofpibogaine reduces thedpatient's noribogainedC max compared to adpatient administered4an effective amount ofaibogaine withoutVadministration of theddrug that inhibits theFmetabolism ofaibogaine.p

*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;P<sup>1</sup>/4.05) and t1/2 longer (20.1 vs. 13.0 hours;P<sup>1</sup>/4.07) 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 lbogaine and Noribogaine Pharmacokinetic Parameters, and Mean Active Molety AUC<sub>0</sub>-e, Following a Single 20 mg Oral Dose of Ibogaine

| Analyte       | Pretreatment                          |                 |                     |       |  |  |
|---------------|---------------------------------------|-----------------|---------------------|-------|--|--|
|               | Parameter                             | Placebo (n = 9) | Paroxetine (n = 11) | Р     |  |  |
| Ibogaine      | AUC <sub>D-c</sub> (ng · h/mL)        | 3.6 (7.2)       | 238.2 (202.1)       | .0028 |  |  |
|               | Cmas (ng/mL)                          | 1.1 (1.8)       | 29.5 (16.8)         | <.000 |  |  |
|               | T <sub>max</sub> (hours)*             | 1.0 (0-3)       | 1.5 (0-3)           | .17   |  |  |
|               | t <sub>4/2</sub> (hours)              | 2.5 (0.9)       | 10.2 (7.8)          | .009  |  |  |
| Noribogaine   | AUCp-t (ng h/mL)                      | 277.4 (116.9)   | 304.1 (127.9)       | .64   |  |  |
|               | C <sub>max</sub> (ng/mL)              | 18.7 (7.3)      | 12.7 (5.3)          | .05   |  |  |
|               | T <sub>max</sub> (hours) <sup>a</sup> | 4.0 (2-4)       | 3.0 (1.5-8)         | .63   |  |  |
|               | t <sub>1/2</sub> (hours)              | 13.0 (4.7)      | 20.1 (10.2)         | .07   |  |  |
| Active moiety | AUCo-r (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 placebopretreated subjects, paroxetine-pretreated subjects had rapid** (**Tmax<sup>1</sup>/41.5 hours) and substantial absorption of ibogaine**, with detectable levels out to 72 hours, and an elimination half-life of 10.2 hours."

|  | 5 PALIL (201   | 9) "Introduction t  | o Basics of Pharm  | acology and Toxic  | ology"                        |
|--|--|---|--|--|-------------------------------|
|  | Springer. page   | · ·   |  | acology and Toxic  | ology                         |
|  | Bioavailabili<br>bioavailability   | ty is the extent to   | which absorption<br>the administered                               | n terms of bioavail<br>n occurs. In other w<br>drug that reaches th                    | words,                        |
| 23. The method of<br>claim 21, wherein the<br>patient's noribogaine<br>C max is reduced by<br>about 5% to about<br>30% compared to the<br>patient administered | From the application of interest, 17/941,648, paragraph [0010] "In some<br>embodiments, the drug that inhibits the metabolism of ibogaine is a CYP2D6<br>inactivator. In some embodiments, <b>the CYP2D6 inactivator is selected from</b><br>the group consisting of 3,4-Methylenedioxymethamphetamine (MDMA),<br><b>paroxetine</b> , cimetidine, pimozide, methamphetamine, metoclopramide or<br>desethylamiodarone." |   |  |  |                               |
| the effective amount of<br>ibogaine without<br>administration of the<br>drug that inhibits the<br>metabolism of  | 4. GLUE (2015) "Influence of CYP2D6 Activity on the Pharmacokinetics<br>and Pharmacodynamics of a Single 20 mg Dose of Ibogaine in Healthy<br>Volunteers" Pharmacokinetics/Pharmacodynamics. Vol. 55(6) 680-687.   |   |  |  |                               |
| ibogaine.  | appears to be<br>pharmacokine<br><b>ibogaine in 2</b>  | mediated primaril   | y by CYP2D6. We<br>h analytes after <b>a</b> s<br>s who had been p | ive metabolite nori<br>e compared 168 ho<br>single oral 20 mg o<br>pretreated for 6 da | urs<br>lose of                |
|  | in both group  | s, mean <b>Cmax wa</b>  | s lower (12.7 vs.  | JCO–t values were s<br>18.7 ng/mL;P <sup>1</sup> /4.05                                 |                               |
|  |  | 20.1 vs. 13.0 hours<br>th placebo-pretre  | · · •  | -  |                               |
|  |  |   |  | Noribogaine Pharmacokinetic Param  | eters, and Mean               |
|  |  | 0 <del></del>   | Pretreatme   | nt   |                               |
|  | Analyte  | Parameter   | Placebo (n = 9)  | Paroxetine (n = 11)  | P<br>.0028                    |
|  | Ibogaine   | AUC <sub>D+s</sub> (ng h/mL)<br>C <sub>max</sub> (ng/mL)<br>T <sub>mix</sub> (hours)* | 3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)                                | 238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)  | <.0001<br>_17                 |
|  | Noribogaine  | t <sub>4/2</sub> (hours)<br>AUC <sub>0-t</sub> (ng h/mL)<br>C <sub>max</sub> (ng/mL)  | 2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)                           | 10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)  | .009<br>.64<br>.05            |
|  |  | T <sub>mus</sub> (hours)"<br>t <sub>1/2</sub> (hours)                                 | 4.0 (2-4)<br>13.0 (4.7)  | 3.0 (1.5-8)<br>20.1 (10.2)   | .63                           |
|  | Active molety  | AUC <sub>0-c</sub> (nM · h/mL)  | 948 (407)  | 1793 (695)   | .07<br>.005                   |
|  | Active moiety<br>  | AUC <sub>0-c</sub> (nM · h/mL)  | 948 (407)  | (649)  | .07                           |
| 24. The method of  | "Median (range).   |   | 0.000  | agraph [0010] "In  | .07<br>.005                   |
| 24. The method of claim 1, wherein the   | <sup>*Median (range).</sup><br>From the app  | lication of interest  | , 17/941,648, para   | 000.00.00  | .07<br>.005                   |
|  | Median (range).<br>From the app<br>embodiments,  | lication of interest<br>the drug that inhi  | , 17/941,648, part<br>bits the metabolis                           | agraph [0010] "In  | .07<br>.005<br>some<br>CYP2D6 |

|  |  |  |  |  | 1   |  |  |
|--|--|--|--|--|---|--|--|
| metabolism of  | paroxetine,  | cimetidine, pimozido   | e, methamphetam  | ine, metoclopramia   | le or   |  |  |
| ibogaine increases the   | desethylami  | odarone."  | -  | -  |   |  |  |
| patient's ibogaine C   |  |  |  |  |   |  |  |
| - 0  |  |  |  |  |   |  |  |
| max compared to a  |  |  |  |  |   |  |  |
| patient administered   | 4. GLUE (20  | 015) "Influence of C   | CYP2D6 Activity  | on the Pharmacoki  | netics  |  |  |
| an effective amount of   | and Pharmad  | codynamics of a Sin  | gle 20 mg Dose o   | of Ibogaine in Healt   | hv  |  |  |
| ibogaine without   |  | Pharmacokinetics/F   |  | -  | •   |  |  |
| -  | Volunteers   | r narmacokinetics/r  | naimacouynaim  | .s. vol. 55(0) 080-0   | 007.  |  |  |
| administration of the  |  |  |  |  |   |  |  |
| drug that inhibits the   | From page 6  | 680 "Conversion of   | ibogaine to its ac   | tive metabolite nori   | bogaine   |  |  |
| metabolism of  | appears to be  | e mediated primarily   | y by CYP2D6. W   | e compared 168 ho  | urs   |  |  |
| ibogaine.  | · •  | netic profiles of both   | •  | •  |   |  |  |
|  |  |  |  |  |   |  |  |
|  |  | 21 healthy subjects  |  | pretreated for 6 da  | iys with  |  |  |
|  | placebo or t   | the CYP2D6 inhibi  | tor paroxetine"  |  |   |  |  |
|  |  |  |  |  |   |  |  |
|  | From <b>page</b> (   | 586 "In placebo-pre  | etreated subjects  | , ibogaine was ran   | oidly   |  |  |
|  | - 0  | o noribogaine, with  | •  |  | •   |  |  |
|  |  | 0 ,  |  | 0  |   |  |  |
|  | •  | 4 hours post dose.   | •  | •  |   |  |  |
|  | occurred by  | 4 hours. Compared  | with placebo-pre   | treated subjects, su   | bjects  |  |  |
|  | who had ree  | duced CYP2D6 act   | ivity from paroy   | ketine pretreatmen   | t had   |  |  |
|  |  |  | • •  | -  |   |  |  |
|  | rapid (median Tmax <sup>1</sup> / <sub>4</sub> 1.5 hours) and substantial absorption of ibogaine,  |  |  |  |   |  |  |
|  |  | with detectable levels out to72 hours, and an elimination half-life of 10.2  |  |  |   |  |  |
|  |  | able levels out to72   | hours, and an el   | imination half-life of   | of 10.2   |  |  |
|  | with detecta<br>hours."  | able levels out to72   | hours, and an el   | imination half-life of   | of 10.2   |  |  |
|  |  | able levels out to72   | hours, and an el   | imination half-life o  | of 10.2   |  |  |
|  | hours."  |  | hours, and an el   | imination half-life of   | of 10.2   |  |  |
|  | hours."<br>From <b>page (</b>  | 584  |  |  |   |  |  |
|  | hours."<br>From <b>page (</b><br>Table I. Influence o  |  | on Mean (SD) Plasma Ibogaine and   |  |   |  |  |
|  | hours."<br>From <b>page (</b><br>Table I. Influence o  | 584<br>1 Placebo or Paroxetine Pretreatment of   | on Mean (SD) Plasma Ibogaine and   | i Noribogaine Pharmacokinetic Param  |   |  |  |
|  | hours."<br>From <b>page (</b><br>Table I. Influence o  | 584<br>1 Placebo or Paroxetine Pretreatment of   | on Mean (SD) Plasma Ibogaine and<br>of Ibogaine  | i Noribogaine Pharmacokinetic Param  |   |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo   | 584<br>(Placebo or Paroxetine Pretreatment or<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bes</sub> (ng-h/mL)   | on Mean (SD) Plasma lbogaine and<br>of Ibogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (7.2)   | I Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)   | eters, and Mean   |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte  | 584<br>(Placebo or Paroxetine Pretreatment o<br>or Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng -h/mL)<br>C <sub>max</sub> (ng/mL)  | on Mean (SD) Plasma Ibogaine and<br>of Ibogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)  | l Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)  | P<br>.0028<br><.0001  |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte  | 584<br>(Placebo or Paroxetine Pretreatment or<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bes</sub> (ng-h/mL)   | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.9 (0-3)<br>2.5 (0.9)  | I Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)   | eters, and Mean   |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte  | 584<br>(Placebo or Paroxetine Pretreatment or<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>fret</sub> (ng-h/mL)<br>Cmax (ng/mL)<br>Tmax (nours)*<br>t <sub>10</sub> (hours)<br>AUC <sub>6-t</sub> (ng-h/mL)  | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)   | I Noribogaine Pharmacokinetic Param<br>ent.<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)   | P<br>.0028<br><.0001<br>.17<br>.009<br>.64  |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo.  | 584<br>f Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>Det</sub> (ng-h/mL)<br>C <sub>max</sub> (nours)*<br>t <sub>1/2</sub> (hours)   | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.9 (0-3)<br>2.5 (0.9)  | I Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)   | P<br>.0028<br><.0001<br>.17<br>.009   |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo,<br>Analyte<br>Ibogaine   | 584<br>(Placebo or Paroxetine Pretreatment or<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>los</sub> (ng-h/mL)<br>Cmas (ng/mL)<br>Tmas (ng/mL)<br>AUC <sub>0-t</sub> (ng-h/mL)<br>Cmas (ng/mL)<br>Cmas (ng/mL)<br>Tmas (ng/mL)<br>Tmas (nours)*<br>tr(2 (hours)  | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pietreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)  | 1 Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5-6)<br>20.1 (10.2)  | P<br>0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07  |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo.  | 584<br>(Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>Det</sub> (ng-h/mL)<br>Cmax (ng/mL)<br>Tmax (hours) <sup>a</sup><br>tir2 (hours)<br>AUC <sub>det</sub> (ng-h/mL)<br>Cmax (ng/mL)<br>Tmax (hours) <sup>a</sup>   | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)  | I Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5–6)  | P<br>0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63   |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo,<br>Analyte<br>Ibogaine   | 584<br>(Placebo or Paroxetine Pretreatment or<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>los</sub> (ng-h/mL)<br>Cmas (ng/mL)<br>Tmas (ng/mL)<br>AUC <sub>0-t</sub> (ng-h/mL)<br>Cmas (ng/mL)<br>Cmas (ng/mL)<br>Tmas (ng/mL)<br>Tmas (nours)*<br>tr(2 (hours)  | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pietreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)  | 1 Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5-6)<br>20.1 (10.2)  | P<br>0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07  |  |  |
|  | hours."<br>From page (<br>Table I. Influence of<br>Active Molety AUCo.<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).  | 584<br>(Placebo or Paroxetine Pretreatment or<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>(b-c</sub> (ng-h/mL)<br>Cmax (ng/mL)<br>Tmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Tmax (nurs)*<br>tria (hours)<br>AUC <sub>0-c</sub> (nM·h/mL)  | on Mean (SD) Plasma Ibogaine and<br>of Ibogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)   | I Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5-6)<br>20.1 (10.2)<br>1793 (695)  | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005   |  |  |
| 25. The method of  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the ap   | 584<br>f Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng/mL)<br>Tmu (hours)*<br>t <sub>1/2</sub> (hours)<br>AUC <sub>bet</sub> (ng/mL)<br>Cmux (ng/mL)<br>Tmu (hours)*<br>t <sub>1/2</sub> (hours)<br>AUC <sub>bet</sub> (nf/-h/mL)<br>plication of interest,   | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par   | I Noribogaine Pharmacokinetic Param<br>ent<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-6)<br>20.1 (10.2)<br>1793 (695)<br>20.1 (10.1)<br>1793 (695)   | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>.05<br>.63<br>.07<br>.005<br>.05<br>.63<br>.07<br>.005 |  |  |
| 25. The method of<br>claim 24, wherein the   | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the ap   | 584<br>(Placebo or Paroxetine Pretreatment or<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>(b-c</sub> (ng-h/mL)<br>Cmax (ng/mL)<br>Tmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Cmax (ng/mL)<br>Tmax (nurs)*<br>tria (hours)<br>AUC <sub>0-c</sub> (nM·h/mL)  | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par   | I Noribogaine Pharmacokinetic Param<br>ent<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-6)<br>20.1 (10.2)<br>1793 (695)<br>20.1 (10.1)<br>1793 (695)   | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>.05<br>.63<br>.07<br>.005<br>.05<br>.63<br>.07<br>.005 |  |  |
|  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo.<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the apple of the second seco | 584<br>f Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng/mL)<br>Tmu (hours)*<br>t <sub>1/2</sub> (hours)<br>AUC <sub>bet</sub> (ng/mL)<br>Cmux (ng/mL)<br>Tmu (hours)*<br>t <sub>1/2</sub> (hours)<br>AUC <sub>bet</sub> (nf/-h/mL)<br>plication of interest,   | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (72)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par<br>bits the metabolis   | I Noribogaine Pharmacokinetic Param<br>ent.<br>238.2 (202.1)<br>29.5 (16.8)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5-8)<br>20.1 (10.2)<br>1793 (695)<br>20.1 (10.2)<br>1793 (695)  | P<br>.0028<br><.001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>.63<br>.07<br>.005                                      |  |  |
| claim 24, wherein the  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the ap<br>embodiment,<br>inactivator.  | 584<br>(Placebo or Paroxetine Pretreatment of<br>parameter<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cinus (ng/mL)<br>Tinas (hours) <sup>a</sup><br>tir2 (hours)<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cinus (ng/mL)<br>Tinas (hours) <sup>a</sup><br>tir2 (hours)<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cinus (ng/mL)<br>Tinas (hours) <sup>a</sup><br>tir2 (hours)<br>AUC <sub>bet</sub> (nM-h/mL)<br>plication of interest,<br>s, the drug that inhibit  | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Placebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par<br>bits the metabolis<br>ts, <b>the CYP2D6</b> i  | 1 Noribogaine Pharmacokinetic Param<br>ent.<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5-6)<br>20.1 (10.2)<br>1793 (695)<br>Pagraph [0010] "In<br>sem of ibogaine is a for<br>inactivator is select  | eters, and Mean   |  |  |
| claim 24, wherein the patient's ibogaine C   | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the apple of the group co  | 584<br>(Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cmax (hours)<br>AUC <sub>6-t</sub> (ng/mL)<br>Tmax (hours)<br>AUC <sub>6-t</sub> (ng/mL)<br>Tmax (hours)<br>AUC <sub>6-t</sub> (ng/mL)<br>Tmax (hours)<br>AUC <sub>6-t</sub> (nf/h/mL)<br>plication of interest,<br>s, the drug that inhibit<br>In some embodimen  | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Piacebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par<br>bits the metabolis<br>ts, <b>the CYP2D6 i</b><br>nylenedioxymetho                                | A Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-6)<br>20.1 (10.2)<br>1793 (695)<br>Pagraph [0010] "In<br>sem of ibogaine is a formation of iboga | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>Some<br>CYP2D6<br>ed from<br>IA),                      |  |  |
| claim 24, wherein the<br>patient's ibogaine C<br>max is increased by<br>about 5% to about  | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo.<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the ap<br>embodiment,<br>inactivator<br>the group co<br>paroxetine,   | 584<br>(Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (nM-h/mL)<br>plication of interest,<br>s, the drug that inhite<br>In some embodiment<br>onsisting of 3,4-Meth<br>cimetidine, pimozide | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Piacebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par<br>bits the metabolis<br>ts, <b>the CYP2D6 i</b><br>nylenedioxymetho                                | A Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-6)<br>20.1 (10.2)<br>1793 (695)<br>Pagraph [0010] "In<br>sem of ibogaine is a formation of iboga | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>Some<br>CYP2D6<br>ed from<br>IA),                      |  |  |
| claim 24, wherein the<br>patient's ibogaine C<br>max is increased by<br>about 5% to about<br>30% compared to a                         | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the apple of the group co  | 584<br>(Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (nM-h/mL)<br>plication of interest,<br>s, the drug that inhite<br>In some embodiment<br>onsisting of 3,4-Meth<br>cimetidine, pimozide | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Piacebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par<br>bits the metabolis<br>ts, <b>the CYP2D6 i</b><br>nylenedioxymetho                                | A Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-6)<br>20.1 (10.2)<br>1793 (695)<br>Pagraph [0010] "In<br>sem of ibogaine is a formation of iboga | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>Some<br>CYP2D6<br>ed from<br>IA),                      |  |  |
| claim 24, wherein the<br>patient's ibogaine C<br>max is increased by<br>about 5% to about<br>30% compared to a<br>patient administered | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo.<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the ap<br>embodiment,<br>inactivator<br>the group co<br>paroxetine,   | 584<br>(Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (nM-h/mL)<br>plication of interest,<br>s, the drug that inhite<br>In some embodiment<br>onsisting of 3,4-Meth<br>cimetidine, pimozide | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Piacebo (n = 9)<br>3.6 (7.2)<br>1.1 (1.8)<br>1.0 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par<br>bits the metabolis<br>ts, <b>the CYP2D6 i</b><br>nylenedioxymetho                                | A Noribogaine Pharmacokinetic Param<br>ent<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-6)<br>20.1 (10.2)<br>1793 (695)<br>Pagraph [0010] "In<br>sem of ibogaine is a formation of iboga | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>Some<br>CYP2D6<br>ed from<br>IA),                      |  |  |
| claim 24, wherein the<br>patient's ibogaine C<br>max is increased by<br>about 5% to about<br>30% compared to a                         | hours."<br>From page (<br>Table I. Influence o<br>Active Molety AUCo.<br>Analyte<br>Ibogaine<br>Noribogaine<br>Active molety<br>"Median (range).<br>From the apple of the group cooparoxetine, of the desethylamic   | 584<br>(Placebo or Paroxetine Pretreatment of<br>e Following a Single 20 mg Oral Dose<br>Parameter<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (ng-h/mL)<br>Cnue (ng/mL)<br>Trace (hours) <sup>a</sup><br>tra (hours) <sup>a</sup><br>tra (hours)<br>AUC <sub>bet</sub> (nM-h/mL)<br>plication of interest,<br>s, the drug that inhite<br>In some embodiment<br>onsisting of 3,4-Meth<br>cimetidine, pimozide | on Mean (SD) Plasma lbogaine and<br>of lbogaine<br>Pretreatm<br>Placebo (n = 9)<br>3.6 (72)<br>1.1 (1.8)<br>1.3 (0-3)<br>2.5 (0.9)<br>277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4)<br>13.0 (4.7)<br>948 (407)<br>, 17/941,648, par<br>bits the metabolis<br>ts, <b>the CYP2D6</b> i<br>hylenedioxymetho<br>e, methamphetam | A Noribogaine Pharmacokinetic Param<br>ent.<br>Paroxetine (n = 11)<br>238.2 (202.1)<br>29.5 (16.8)<br>1.5 (0-3)<br>10.2 (7.8)<br>304.1 (127.9)<br>12.7 (5.3)<br>3.0 (15-8)<br>20.1 (10.2)<br>1793 (695)<br>Pagraph [0010] "In<br>sem of ibogaine is a Contractivator is select<br>imphetamine (MDN)<br>paine, metoclopramical  | P<br>.0028<br><.0001<br>.17<br>.009<br>.64<br>.05<br>.63<br>.07<br>.005<br>Some<br>CYP2D6<br>ed from<br>IA),<br>le or             |  |  |

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.

administration of the drug that inhibits the

| metabolism of<br>ibogaine.   | appears to be<br>pharmacokin<br>ibogaine in 2<br>placebo or t<br>From page 6<br>converted to<br>subjects by<br>occurred by<br>who had red<br>rapid (medi<br>with detecta<br>hours."   | e mediated primaril<br>aetic profiles of both<br>21 healthy subject<br>he CYP2D6 inhibit<br>86 "In placebo-pro-<br>o noribogaine, with<br>4 hours post dose.<br>4 hours. Compared<br>luced CYP2D6 act<br>an Tmax <sup>1</sup> /41.5 hou<br>ble levels out to72<br>84 | y by CYP2D6. W<br>h analytes after <b>a</b><br><b>s who had been</b> p<br>itor paroxetine"<br>etreated subjects<br><b>h undetectable ik</b><br>Median peak nor<br>with placebo-pre<br>tivity from parox<br>rs) and substant<br>hours, and an el | tive metabolite nori<br>ve compared 168 ho<br>single oral 20 mg of<br>pretreated for 6 da<br>s, ibogaine was rap<br>bogaine levels in al<br>ibogaine concentration<br>treated subjects, su<br>ketine pretreatment<br>ial absorption of il<br>imination half-life of | ours<br>dose of<br>nys with<br>bidly<br>l<br>tions<br>bjects<br>at had<br>bogaine,<br>of 10.2 |
|--|---|--|---|---|---|
|  | Active Piolety AOCo-  | , Poliowing a single 20 mg Oral Dose   | Pretreatm   | ent   |   |
|  | Analyte   | Parameter  | Placebo (n = 9)   | Paroxetine (n = 11)   | P   |
|  | Ibogaine  | AUC Dec (ng h/mL)  | 3.6 (7.2)   | 238.2 (202.1)   | .0028   |
|  |   | C <sub>max</sub> (ng/mL)<br>T <sub>max</sub> (hours)*  | 1.1 (1.8)<br>1.0 (0-3)  | 29.5 (16.8)<br>1.5 (0-3)  | <.0001  |
|  | Norikamina  | t <sub>1/2</sub> (hours)   | 2.5 (0.9)   | 10.2 (7.8)  | .009  |
|  | Noribogaine   | AUC <sub>D-t</sub> (ng h/mL)<br>C <sub>max</sub> (ng/mL)   | 277.4 (116.9)<br>18.7 (7.3)   | 304.1 (127.9)<br>12.7 (5.3)   | .64<br>.05  |
|  |   | T <sub>max</sub> (hours) <sup>a</sup><br>t <sub>1/2</sub> (hours)  | 4.0 (2-4)<br>13.0 (4.7)   | 3.0 (1.5-8)<br>20.1 (10.2)  | .63   |
|  | Active moiety<br>"Median (range).   | AUC <sub>0-c</sub> (nM·h/mL)   | 948 (407)   | 1793 (695)  | .005  |
| 26. The method of<br>claim 1, wherein the<br>effective amount of<br>ibogaine administered<br>in combination with a<br>drug that inhibits the<br>metabolism is lower<br>than an effective<br>amount of ibogaine<br>without<br>administration of the | <ul> <li>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.</li> <li>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</li> </ul> |  |   |   |   |
| drug that inhibits the<br>metabolism of<br>ibogaine.   | (Tmax <sup>1</sup> /41.5  | hours) and substa<br>vels out to 72 hours  | ntial absorption  | eated subjects had<br>of ibogaine, with<br>ion half-life of 10.2  | -   |

|  | Table I. Influence of    | Placebo or Paroxetine Pretreatment  | on Mean (SD) Plasma lbogaine and         | d Noribogaine Pharmacokinetic Param        | eters, and Mean   |
|--|--------------------------|---|--|--|-------------------|
|  |                          | , Following a Single 20 mg Oral Dose  |  |  |                   |
|  | Analyte                  | Parameter   | Pretreatm<br>Placebo (n = 9)             | Paroxetine (n = 11)                        | p                 |
|  | Ibogaine                 | AUC <sub>D-c</sub> (ng·h/mL)<br>C <sub>max</sub> (ng/mL)  | 3.6 (7.2)<br>1.1 (1.8)                   | 238.2 (202.1)<br>29.5 (16.8)               | .0028<br><.0001   |
|  | Manhamima                | T <sub>mix</sub> (hours)*<br>t <sub>4/2</sub> (hours)   | 1.0 (0-3)<br>2.5 (0.9)                   | 1.5 (0-3)<br>10.2 (7.8)                    | .17<br>.009       |
|  | Noribogaine              | AUC <sub>0-t</sub> (ng·h/mL)<br>C <sub>max</sub> (ng/mL)<br>T <sub>max</sub> (hours) <sup>a</sup> | 277.4 (116.9)<br>18.7 (7.3)<br>4.0 (2-4) | 304.1 (127.9)<br>12.7 (5.3)<br>3.0 (1.5–8) | .64<br>.05<br>.63 |
|  | Active molety            | t <sub>1/2</sub> (hours)<br>AUC <sub>0-c</sub> (nM · h/mL)  | 13.0 (4.7)<br>948 (407)                  | 20.1 (10.2)<br>1793 (695)                  | .07<br>.005       |
|  | 'Median (range).         |   |  |  |                   |
| 27. The method of                        | 4. GLUE (20              | ()15) "Influence of C   | CYP2D6 Activity                          | on the Pharmacoki                          | netics            |
| claim 26, wherein the                    |                          | •   | • •                                      | of Ibogaine in Healt                       | •                 |
| effective amount of ibogaine is about 5% | Volunteers"              | Pharmacokinetics/I  | harmacodynamic                           | cs. Vol. 55(6) 680-6                       | 687.              |
| to about 50% lower                       | From page 6              | 80 "Conversion of   | ibogaine to its ac                       | tive metabolite nori                       | bogaine           |
| than an effective                        | - 0                      |   | e  | e compared 168 ho                          | •                 |
| amount of ibogaine                       | pharmacokin              | netic profiles of both  | n analytes after <b>a</b>                | single oral 20 mg o                        | lose of           |
| without                                  | ibogaine in 2            | 21 healthy subjects   | s who had been j                         | pretreated for 6 da                        | ys with           |
| administration of the                    | placebo or t             | he CYP2D6 inhibi  | tor paroxetine. I                        | In placebo-pretrea                         | ted               |
| drug that inhibits the                   | subjects, ibo            | ogaine was rapidly  | converted to no                          | ribogaine. Median                          | peak              |
| metabolism of                            | noribogaine              | concentrations oc   | curred at 4 hour                         | rs. Compared with                          |                   |
| ibogaine.                                | placebo-pre              | treated subjects, p   | aroxetine-pretro                         | eated subjects had                         | rapid             |
|  | (Tmax <sup>1</sup> /41.5 | hours) and substa   | ntial absorption                         | of ibogaine, with                          |                   |
|  | detectable le            | vels out to 72 hours  | , and an eliminat                        | ion half-life of 10.2                      | hours."           |
|  |                          |   |  |  |                   |
|  | From page 6              | 84  |  |  |                   |
|  |                          | Placebo or Paroxetine Pretreatment<br>, Following a Single 20 mg Oral Dose                        |  | d Noribogaine Pharmacokinetic Param        | eters, and Mean   |
|  |                          | , ronowing a single zo ing oral bose  | Pretreatm                                | ent  |                   |
|  | Analyte                  | Parameter   | Placebo (n = 9)                          | Paroxetine (n = 11)                        | Р                 |
|  | Ibogaine                 | AUC <sub>D-s</sub> (ng - h/mL)<br>C <sub>max</sub> (ng/mL)  | 3.6 (7.2)<br>1.1 (1.8)                   | 238.2 (202.1)<br>29.5 (16.8)               | .0028<br><.0001   |
|  |                          | T <sub>mix</sub> (hours)*<br>t <sub>1/2</sub> (hours)   | 1.0 (0-3)<br>2.5 (0.9)                   | 1.5 (0-3)<br>10.2 (7.8)                    | .17<br>.009       |
|  | Noribogaine              | AUC <sub>0-e</sub> (ng h/mL)  | 277.4 (116.9)                            | 304.1 (127.9)                              | .64               |
|  |                          | C <sub>max</sub> (ng/mL)<br>T <sub>max</sub> (hours) <sup>a</sup>                                 | 18.7 (7.3)<br>4.0 (2-4)                  | 12.7 (5.3)<br>3.0 (1.5-8)                  | .05<br>.63        |
|  | Active molety            | t <sub>i/2</sub> (hours)<br>AUC <sub>0-c</sub> (nM · h/mL)  | 13.0 (4.7)<br>948 (407)                  | 20.1 (10.2)<br>1793 (695)                  | .07               |
|  | "Median (range).         |   | 5270 <b>4</b> 000 <b>1</b>               | 1.000000.0000.00                           |                   |
|  | ,,                       |   |  |  |                   |
| 28. The method of                        | 4. GLUE (20              | ()15) "Influence of C   | CYP2D6 Activity                          | on the Pharmacoki                          | netics            |
| claim 1, wherein the                     | · ·                      | <i>,</i>  | •  | of Ibogaine in Healt                       |                   |
| effective amount of                      |                          | •   | • •                                      | cs. Vol. 55(6) 680-6                       | •                 |
| ibogaine is about 20                     |                          |   | 2  |  |                   |
| mg to about 1000 mg.                     | From <b>page 6</b>       | 80 "Conversion of   | ibogaine to its ac                       | tive metabolite nori                       | bogaine           |
|  |                          |   | <b>U</b>                                 | e compared 168 ho                          | •                 |
|  |                          |   | •  | single oral 20 mg of                       |                   |
|  | <b>^</b>                 | •   | •  | pretreated for 6 da                        |                   |
|  | 0                        | he CYP2D6 inhibi  | -  | -  | ys with           |
|  | I DIACEDO OF L           | ne u i r 2D0 mmilli   | tor paroxetine.                          |  |                   |

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

| Electronic Acl                       | Electronic Acknowledgement Receipt |  |  |  |  |  |
|--------------------------------------|------------------------------------|--|--|--|--|--|
| EFS ID:                              | 47951593                           |  |  |  |  |  |
| Application Number:                  | 17941648                           |  |  |  |  |  |
| International Application Number:    |                                    |  |  |  |  |  |
| Confirmation Number:                 | 4913                               |  |  |  |  |  |
| Title of Invention:                  | IBOGAINE COMBINATION TREATMENT     |  |  |  |  |  |
| First Named Inventor/Applicant Name: | Srinivas G. RAO                    |  |  |  |  |  |
| Customer Number:                     | 58249                              |  |  |  |  |  |
| Filer:                               | Shahin Shams                       |  |  |  |  |  |
| Filer Authorized By:                 |                                    |  |  |  |  |  |
| Attorney Docket Number:              | ATAI-017/01US 338067-2044          |  |  |  |  |  |
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# Payment information:

| Submitted with Payment                            | yes  |
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| Payment Type                                      | CARD   |
| Payment was successfully received in RAM          | \$72   |
| RAM confirmation Number                           | E202354E14569108   |
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| Document<br>Number | Document Description   | File Name                                  | File Size(Bytes)/<br>Message Digest          | Multi<br>Part /.zip | Pages<br>(if appl.) |
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|                    |  |  | 40470  |                     |                     |
| 1                  | Concise Description of Relevance                                     | Concise-description-generated.<br>pdf      | 48f56f235d16aab95a923a00f58644aac73c<br>dbe0 | no                  | 5                   |
| Warnings:          |  |  |  |                     |                     |
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|                    |  |  | 64617  |                     |                     |
| 2                  | Third-Party Submission Under 37 CFR<br>1.290                         | Third-party-preissuance-<br>submission.pdf | c1f7441f27926ebe8d003c898e53cf2e1da4<br>eecb | no                  | 3                   |
| Warnings:          |  |  |  |                     |                     |
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|                    |  |  | 23720  |                     |                     |
| 3                  | Request for Notification of Non-<br>compliant Third-Party Submission | Third-party-notification-<br>request.pdf   | 273b58a2b1d5394ac50708e97a5e0cdd512<br>36cb7 | no                  | 1                   |
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|                    |  |  | 213347                                       |                     |                     |
| 4                  | Concise Description of Relevance                                     | US20230100844ClaimChartCo<br>mp.pdf        | ba8c2afd60b74f5c543f70a10c42f8285c0ea<br>910 | no                  | 23                  |
| Warnings:          |  |  |  | I                   |                     |
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|                    |  |  | 959937                                       |                     |                     |
| 5                  | Evidence of Publication  | 1-WO2000059486.pdf                         | 7f87d5f4b2654a1b5a63bdbfb0ccde0792bf<br>4657 | no                  | 18                  |
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| 6                  | Evidence of Publication  | 2-WO2001052851.pdf                         | 2dbc8ed421037b67eccd454a2ed3a7436a7<br>503c5 | no                  | 48                  |
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| 11           | Fee Worksheet (SB06)    | fee-info.pdf               | 1a2731a46a14a80088a87eaf1ba6bd4abfa6<br>3806 | no    | 2   |
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| 10           | Evidence of Publication | 6-Henstra.pdf              | 481b1f67f7940dc6cc1a64344e4d4fe6c200<br>528a | no    | 4   |
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| Warnings:    |                         | Į                          |  |       |     |
| 9            | Evidence of Publication | 5-Paul.pdf                 | c19a5c8c1411e44c137d874d87524e48122<br>81101 | no    | 410 |
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| 8            | Evidence of Publication | 4-GLUE.pdf                 | c25e0acca6ccdf80c9c167d261e74e4ce560<br>d5d4 | no    | 8   |
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| Information: |                         |                            |  |       |     |
| Warnings:    |                         |                            |  |       |     |
| 7            | Evidence of Publication | 3-WO2023012691.pdf         | 1605728d00ddbf2fa9ae6aad96bb7b03425<br>3f5c7 | no    | 136 |
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### New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.