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(71) Applicant: **DEMEXX, INC.** [US/US]; 305 South Andrews Avenue, Suite 515, Fort Lauderdale, Florida 33301 (US).

(72) Inventor: **FRIEDHOFF, Lawrence**; c/o Demerx, Inc., 305 South Andrews Avenue, Suite 515, Fort Lauderdale, Florida 33301 (US).

(74) Agents: **SWISS, Gerald F.** et al.; c/o Foley & Lardner LLP, 3000 K Street N.W., Suite 600, Washington, District of Columbia 20007-5109 (US).

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(54) Title: METHOD FOR NON-TOXIC TREATMENT FOR DRUG WITHDRAWAL

(57) Abstract:



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METHOD FOR NON-TOXIC TREATMENT FOR DRUG WITHDRAWAL

BACKGROUND

[0001] The disclosure relates to the treatment of drug withdrawal symptoms.

[0002] Withdrawal from drug dependence is characterized by dramatic and traumatic symptoms, including sweating, racing heart, palpitations, muscle tension, tightness in the chest, difficulty breathing, tremor, nausea, vomiting, diarrhea, grand mal seizures, heart attacks, strokes, hallucinations and delirium tremens (DTs). Numerous treatments have been developed in attempts to ameliorate such symptoms.

[0003] Ibogaine has been used as a botanical preparation from the root bark of iboga tabernathe for over 100 years both as a crude preparation and as semisynthetic ibogaine, which was marketed in France until about 1970. Observations in the 1970's suggested that ibogaine in higher doses was useful as a treatment for addiction. The use of ibogaine as a treatment for addiction was controversial because higher doses caused hallucinations and, in spite of many anecdotal reports of striking efficacy, no double-blind, placebo-controlled trials supported the efficacy of ibogaine as a treatment for withdrawal or addiction.

[0004] US Patent No. 6,348,456 discloses highly purified noribogaine and teaches that it should be provided at dosages from about 0.01 to about 100 mg per kg body weight per day.

[0005] More recently, the pharmacokinetics and metabolism of ibogaine was evaluated and it was found that the psychotomimetic effects correlated with blood levels of ibogaine, while the anti-addictive effects correlated with blood levels of noribogaine, the only metabolite of ibogaine found in humans, dogs, rats and monkeys. These experiments were followed up with animal studies of noribogaine in various addiction models, which demonstrated that noribogaine significantly reduced drug-seeking behavior and had no activity in an evaluation of psychotomimetic effects in an animal model. Noribogaine is now being developed as a treatment for the symptoms of drug addiction and has shown to be effective in animal models of addiction to alcohol, cocaine and opiate dependence.

[0006] During pre-clinical toxicity studies in various animal species, it was found that high doses of noribogaine can cause convulsions and other CNS-related clinical signs, respiratory arrest and death. Given the signs of efficacy that noribogaine has shown, there is a need for a

method to administer noribogaine in dosages that provide efficacy without leading to any significant deleterious clinical signs.

SUMMARY

[0007] The disclosure provides a method to administer noribogaine to a human patient having drug addiction in dosages that provide efficacy without leading to any significant deleterious clinical signs. Such dosages provide maximum serum concentrations ($C_{\max}$) of noribogaine of less than about 2000 ng/mL, while maintaining efficacious average noribogaine serum levels of between about 100-2000 ng/mL (AUC/T).

[0008] One embodiment of disclosure provides a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1980 ng/mL serum and an average AUC/24 hr of about 1,100 ng/mL.

[0009] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1800 ng/mL serum and an AUC/24 hr of about 1000 ng/mL.

[0010] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1620 ng/mL serum and an AUC/24 hr of about 900 ng/mL.

[0011] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1440 ng/mL serum and an AUC/24 hr of about 800 ng/mL.

[0012] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1260 ng/mL serum and an AUC/24 hr of about 700 ng/mL.

[0013] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 1400 ng/mL serum and an AUC/24 hr of from about 600 ng/mL.

[0014] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 900 ng/mL serum and an AUC/24 hr of about 500 ng/mL.

[0015] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 720 ng/mL serum and an AUC/24 hr of about 400 ng/mL.

[0016] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 540 ng/mL serum and an AUC/24 hr of about 300 ng/mL.

[0017] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 360 ng/mL serum and an AUC/24 hr of about 200 ng/mL.

[0018] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 180 ng/mL serum and an AUC/24 hr of about 100 ng/mL.

[0019] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 100 mg to about 600 mg at intervals of about 24 hours.

[0020] In some embodiments, the patient is administered a dosage of noribogaine from about 100 mg to about 500 mg at intervals of about 24 hours. In some embodiments, the patient is administered a dosage of noribogaine from about 100 mg to about 400 mg at intervals of about 24 hours. In some embodiments, the patient is administered a dosage of noribogaine from about 100 mg to about 300 mg at intervals of about 24 hours. In some embodiments, the patient is administered a dosage of noribogaine from about 100 mg to about 200 mg at intervals of about 24 hours.

[0021] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 200 mg to about 600 mg at intervals of about 24 hours.

[0022] In some embodiments, the patient is administered a dosage of noribogaine from about 200 mg to about 500 mg at intervals of about 24 hours. In some embodiments, the patient is administered a dosage of noribogaine from about 200 mg to about 400 mg at intervals of about 24 hours. In some embodiments, the patient is administered a dosage of noribogaine from about 200 mg to about 300 mg at intervals of about 24 hours.

[0023] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 300 mg to about 600 mg at intervals of about 24 hours.

[0024] In some embodiments, the patient is administered a dosage of noribogaine from about 300 mg to about 500 mg at intervals of about 24 hours. In some embodiments, the patient is administered a dosage of noribogaine from about 300 mg to about 400 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 400 mg to about 500 mg at intervals of about 24 hours.

[0025] Also provided, in one embodiment, is a method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 500 mg to about 600 mg at intervals of about 24 hours.

BRIEF DESCRIPTION OF THE FIGURES

[0026] FIG. 1 represents mean noribogaine concentration-time profiles after single oral dosing with 3, 10, 30 or 60 mg doses. Inset: Individual concentration-time profiles from 0-12 h after a 10 mg dose.

[0027] FIG. 2 represents mean plasma noribogaine glucuronide concentration-time profiles after single oral 30 or 60 mg doses.

[0028] FIG. 3 represents mean noribogaine concentration-time profile in opioid-addicted patients after single oral 60 mg dose of noribogaine (gray diamonds). Mean noribogaine concentration-time profile in opioid-addicted patients after single oral 120 mg dose of noribogaine (black squares) was estimated based on values for patients receiving 60 mg dose.

[0029] FIG. 4A represents hours to resumption of opioid substitution treatment in patients given no treatment (light gray bar), or a single dose of noribogaine or placebo (60 mg, dark gray bar; 120 mg, black bar). Error bars represent standard deviation.

[0030] FIG. 4B represents the estimated serum noribogaine concentration in ng/mL at time of resumption of opioid substitution treatment (OST) in patients receiving single oral 60 mg dose of noribogaine (gray diamonds) or single oral 120 mg dose of noribogaine (black squares).

[0031] FIG. 5A represents hours to resumption of opioid substitution treatment in patients given no treatment (light gray bar), or a single 120 mg dose of noribogaine (black bar). Error bars represent standard deviation.

[0032] FIG. 5B represents the estimated serum noribogaine concentration in ng/mL at time of resumption of opioid substitution treatment (OST) in patients receiving single oral 120 mg dose of noribogaine (black squares).

DETAILED DESCRIPTION

[0033] The disclosure provides a method to administer noribogaine to a human patient having drug addiction in dosages that provide efficacy without leading to any significant deleterious clinical signs. Such dosages provide maximum serum concentrations (C_{max}) of noribogaine of less than about 2000 ng/mL, while maintaining efficacious average noribogaine serum levels of between about 100-1100 ng/ml (AUC/24 hr).

[0034] The term “noribogaine” as used herein, refers to noribogaine as well as its pharmaceutically acceptable salts. In some embodiments, the methods of the present disclosure entail the administration of a prodrug of noribogaine that provides the desired maximum serum concentrations and efficacious average noribogaine serum levels. A prodrug of noribogaine refers to a compound that metabolizes, *in vivo*, to noribogaine. In some embodiment, the prodrug is selected to be readily cleavable either by a cleavable linking arm or by cleavage of the prodrug entity that binds to noribogaine such that noribogaine is generated *in vivo*. In one preferred embodiment, the prodrug moiety is selected to facilitate binding to the μ and/or κ receptors in the brain either by facilitating passage across the blood brain barrier or by targeting brain receptors other than the μ and/or κ receptors. Examples of prodrugs of noribogaine are provided in United States Patent Application Serial No. 13/165626, the content of which is incorporated here by reference.

[0035] The following ranges are obtained from a single dose of noribogaine HCl/ fasting patient.

[0036] In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 1980 ng/mL serum and an average AUC/24 hr of about 1,100 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 1800 ng/mL serum and an AUC/24 hr of about 1000 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 1620 ng/mL serum and an AUC/24 hr of about 900 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 1440 ng/mL serum and an AUC/24 hr of about 800 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 1260 ng/mL serum and an AUC/24 hr of about 700 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 1400 ng/mL serum and an AUC/24 hr of from about 600 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 900 ng/mL serum and an AUC/24 hr of about 500 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 720 ng/mL serum and an AUC/24 hr of about 400 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 540 ng/mL serum and an AUC/24 hr of about 300 ng/mL. In certain embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 360 ng/mL serum and an AUC/24 hr of about 200 ng/mL. In certain

embodiments, the dosages administered provide a C_{max} of noribogaine of less than about 180 ng/mL serum and an AUC/24 hr of about 100 ng/mL.

[0037] In some embodiments such concentrations are obtained by administering from about 100 to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 200 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 300 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 400 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 500 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 600 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 700 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 800 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 900 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 1,000 mg to about 1,100 mg at intervals of about 24 hours.

[0038] In some embodiments such concentrations are obtained by administering from about 100 mg to about 1,100 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 1,000 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 900 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 800 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 700 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 600 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 500 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 400 mg at intervals of about 24 hours. In some embodiments such concentrations

are obtained by administering from about 100 mg to about 300 mg at intervals of about 24 hours. In some embodiments such concentrations are obtained by administering from about 100 mg to about 200 mg at intervals of about 24 hours.

[0039] Particularly preferred embodiments include the following dose ranges. In some embodiments each patient is administered from about 100 mg to about 600 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 100 mg to about 500 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 100 mg to about 400 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 100 mg to about 300 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 100 mg to about 200 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 200 mg to about 600 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 200 mg to about 500 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 200 mg to about 400 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 200 mg to about 300 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 300 mg to about 400 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 300 mg to about 500 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 300 mg to about 600 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 400 mg to about 500 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 400 mg to about 600 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 500 mg to about 600 mg at intervals of about 24 hours.

[0040] In some embodiments, the patient is administered periodically, such as once, twice, three time, four times or five time daily with noribogaine or its prodrug. In some embodiments, the administration is once daily, or once every second day, once every third day, three times a week, twice a week, or once a week. The dosage and frequency of the administration depends on the route of administration, content of composition, age and body

weight of the patient, condition of the patient, without limitation. Determination of dosage and frequency suitable for the present technology can be readily made a qualified clinician.

[0041] These dose ranges are achieved by oral administration of noribogaine or its prodrug, which may conveniently be provided in tablet, caplet, liquid or capsule form. In certain embodiments, the noribogaine is provided as noribogaine HCl, with dosages reported as the amount of free base noribogaine. In some embodiments, the noribogaine HCl is provided in hard gelatin capsules containing only noribogaine HCl with no excipients.

[0042] Without wishing to be bound by theory, it is believed that noribogaine provides its anti-withdrawal symptom effects by acting as both an $\alpha 3\beta 4$ nicotinic receptor and a serotonin reuptake blocker acting on the 5-HT Transporter.

[0043] The following Examples are intended to further illustrate certain embodiments of the disclosure and are not intended to limit its scope.

Example 1

Single dose toxicity in rats

[0044] The objective of this study was to determine the toxicity and toxicokinetic profile of noribogaine HCl following a single oral (gavage) administration in the Sprague-Dawley rat. A single dose of 100, 300 and 800 mg/kg (achieved with doses of 400 mg/kg 3 h +/- 30 min apart because of the limitations of maximum dose formulation concentration). Five male rats/group were used. Mortality occurred in all male rats in the 800 mg/kg group, approximately 2-3 h after administration of the second dose of 400 mg/kg. Hypoactivity, vocalization, chewing movements, changes in respiration/posture, salivation, stimuli sensitivity, tremors, twitches and penile erection occurred prior to death. Hypoactivity, vocalization, salivation, stimuli sensitivity, loss of limb function and lying on the cage floor occurred on the day of treatment and persisted until Day 2 in 3/5 rats given 300 mg/kg. The low dose rats treated at 100 mg/kg did not show any treatment related signs. The NOAEL was determined to be 100 mg/kg.

Example 2

Single dose toxicity in dogs

[0045] In an acute oral toxicity/TK study in dogs, no mortality occurred at doses of 5 (n=2) or 10 (n=2) mg/kg. Convulsions and other CNS-related clinical signs, including twitches, salivation, vocalization, incoordination and hypoactivity, occurred at a dose of 10 mg/kg, beginning 20 minutes after dosing and persisting until 3h 40m post-dose. The 5 mg/kg dose was considered the NOAEL, as only transient reduction in food consumption in one dog occurred at that dose.

Example 3

Single dose toxicity in Cynomolgus Monkeys

[0046] The objective of the study was to determine the toxicity and toxicokinetic profile of noribogaine following oral (gavage) administration to the cynomolgus monkey. The test article was administered as follows in Table 1:

Table 1. Toxicity and Toxicokinetic Study in Cynomolgus monkeys

Treatment on Study Day	Dose Level (mg/kg)	Number of Animals
1	20	2 males
8	40	2 males
15	80 and 160	2 males

* = Each dose was followed by a 7 day washout period. Dosing was staggered by 45 minutes.

** = One animal was administered 80 mg/kg and the other animal was administered 160 mg/kg.

[0047] Parameters monitored on the study included: mortality, clinical signs and body weights. Blood samples were collected for TK evaluation. No mortality or treatment related clinical signs were noted for doses up to and including 160 mg/kg. The single dose maximum tolerated dose (MTD) was determined to be greater than 160 mg/kg based on the parameters monitored during the study.

Example 4

Fourteen day repeat dose toxicity and toxicokinetics in rats

[0048] This study was conducted to evaluate the toxicity profile of noribogaine-HCl following oral (gavage) administration to the rat for 14 days following Table 2 below:

Table 2. Toxicity and Toxicokinetic Study in Rats

Group	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Toxicology Animals				Toxicokinetics	
			Main		Recovery		Animals	
			Male	Female	Male	Female	Male	Female
Control	0	0	10	10	5	5	3	3
Low Dose	25	5	10	10	-	-	6	6
Mid Dose	50	10	10	10	-	-	6	6
High Dose	100	20	10	10	5	5	6	6

[0049] Male and female Sprague-Dawley rats, 10/sex/group, were administered 0, 25, 50 or 100 mg/kg noribogaine HCl daily by single oral gavage for 14 days. An additional 5 rats/sex/group in the 0 (control) and 100 mg/kg groups were retained for a 28 day recovery period during which no drug was administered. Six rats/sex/group (3 rats/sex controls) were similarly dosed and sampled on study days 1 and 14 for analysis of noribogaine-HCl concentrations in the blood. Rats were observed for mortality, clinical signs, body weight, food consumption, ophthalmology (pre-dose, during week 2, and at the end of recovery), hematology, coagulation, clinical chemistry, urinalysis, gross necropsy, organ weights and histopathology (full tissue panel, plus immunocytochemistry of 5 sections of the brain and spinal cord by staining for GFAP and Calbindin). There were no test article-related effects on mortality (none occurred), clinical signs, ophthalmoscopy, hematology, coagulation parameters, clinical chemistry, urinalysis, gross necropsy or histopathology. Food consumption and body weight were slightly reduced (food consumption: -4.7% in males and females; body weight: -5.5% in males and -2.6% in females) in the high dose (100 mg/kg) groups. Minor increases in liver weight in the mid- and high dose groups were not correlated with histopathologic changes and are considered incidental. No treatment-related differences in the brain were seen in sections stained for GFAP or Calbindin.

[0050] The NOAEL dose in this study was interpreted to be 100 mg/kg, the highest dose tested in the study.

Example 5

Fourteen day repeat dose toxicity and toxicokinetics in dogs

[0051] The objective of this study was to determine the toxicity profile of noribogaine HCl given following oral (gavage) administration to dogs for 14 days according to the following Table 3 below:

Table 3. Toxicity and Toxicokinetic Study in Dogs

Group Designation	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Toxicology Animals			
			Main		Recovery	
			Male	Female	Male	Female
Control	0	0	4	4	4	4
Low Dose	0.5	0.1	4	4	-	-
Mid Dose	1.0	0.2	4	4	-	-
High Dose	5.0	1.0	4	4	4	4

[0052] Noribogaine HCl was administered to groups of 4 male and 4 female dogs by single oral gavage daily for 14 days at doses of 0, 0.5, 1.0 and 5.0 mg/kg/day. An additional group of 4 male and 4 female dogs received either the vehicle control or 5.0 mg/kg/day for 14 days and were held for an additional 28 days after cessation of dosing to assess recovery from any potential drug-induced changes. The study was conducted under GLP guidelines and included comprehensive examinations of clinical signs, body weight, clinical pathology parameters, ophthalmologic examinations, ECG recordings and analyses of plasma for bioanalytical measurement of drug levels at appropriate intervals during the study. At the termination of the dosing phase and at the termination of the recovery phase, all dogs were subjected to a complete post-mortem examination including gross examination of major organs and histologic examination of an extensive list of tissues. Additional sections of brain were obtained from cerebrum, cerebellum, brain stem and spinal cord and examined histologically to evaluate potential effects on brain histopathology. In addition, these sections were examined with immunohistochemical stains for GFAP for evidence of gliosis and Calbindin for a more comprehensive examination of cerebellar Purkinje cells. No evidence of adverse effect was observed in any dog from any treatment group during the dosing or recovery phase in clinical observations, body weights, clinical pathological parameters, ophthalmologic examinations, ECG recordings, or gross lesions at necropsy. The results of the plasma drug level measurements at Day 1 and Day 14 of the study are shown in Tables 4 and 5 below. Noribogaine-HCl maximum plasma concentrations (C_{max}) were reached between 0.5 and 0.9 hours post-dosing, following which plasma concentrations gradually decreased over a period

of up to 24 hours, except in the male dogs and female dogs of Group 4, for which significant levels of noribogaine were still detected at 24 h post-dosing on both Days 1 and 14.

[0053] The only target tissue identified in this study was the lacrimal gland of dogs receiving 5 mg/kg/day. The lacrimal gland changes were characterized by slight to moderate atrophy and degeneration of the acinar cells accompanied by slight to moderate accumulation of brown/yellow pigment and infiltration of mononuclear cells. There was an associated mononuclear infiltration in the draining mandibular lymph nodes of affected dogs in this dose group. Despite the appearance of isolated ocular abnormalities in several dogs in this high dose group on ophthalmologic examination, there was no clear association between these ocular signs and the appearance of the lacrimal gland changes suggesting that these morphologic changes did not result in sufficient functional abnormality of the gland to produce physical changes in exterior structures of the eye. There was no clear evidence of local irritation associated with drug treatment in these high dose dogs. No evidence of drug-induced effect was observed in any other tissue including the extensive sections of brain evaluated with conventional histopathology or with immunohistochemistry. Examination of the animals in the recovery group showed clear evidence of regeneration of this lacrimal gland change. While slight atrophy was still evident in the acinar cells of the gland after 28 days off drug, no evidence of continuing and ongoing degeneration or cellular infiltration was observed. The NOAEL in this study was 1 mg/kg/day based on the lacrimal gland changes at 5 mg/kg/day. The results are summarized in Tables 4 and 5.

Table 4. Mean plasma toxicokinetic parameters for noribogaine in male dogs on days 1 and 14

Parameters	Gr 2 – 0.5 mg/kg		Gr 3 – 1.0 mg/kg		Gr 4 – 5.0 mg/kg	
	D1	D14	D1	D14	D1	D14
T _{1/2} (h)	1.3	1.3	1.2	1.8	4.7	6.5
T _{max} (h)	0.7	0.7	0.9	0.8	0.6	0.9
C _{max} (ng/ml)	28.8	29.4	58.6	67.6	693	716
AUC _{0-last} (hr*ng/ml)	46.6	53.2	102.5	172.3	3515.0	6403.3
AUC _{0-24h} (hr*ng/ml)	59.7	64.5	119.8	210.4	3515.0	6403.3
AUC _{0-∞} (hr*ng/ml)	67.8	68.2	120.8	195.7	3630.5	6961.4

Table 5. Mean plasma toxicokinetic parameters for noribogaine in female dogs on days 1 and 14

Parameters	Gr 2 – 0.5 mg/kg		Gr 3 – 1.0 mg/kg		Gr 4 – 5.0 mg/kg	
	D1	D14	D1	D14	D1	D14
T _{1/2} (hr)	1.0	1.1	1.4	1.6	4.3	5.7
T _{max} (hr)	0.5	1.0	0.8	0.5	0.6	0.6
C _{max} (ng/ml)	25.3	29.8	68.5	74.1	691	683
AUC _{0-last} (hr*ng/ml)	31.5	35.4	148.9	169.0	3367.9	5951.2
AUC _{0-24h} (hr*ng/ml)	40.4	55.0	176.2	203.7	3367.9	5951.2
AUC _{0-∞} (hr*ng/ml)	44.9	45.7	165.3	197.0	3425.7	6283.2

Example 6

Human Pharmacokinetic studies

[0054] In double blind studies, fasting healthy volunteers (6 per cohort) were treated once orally with a tablet of noribogaine HCl. In escalating cohorts, the volunteers received 3 mg, 10 mg, 30 mg or 60 mg noribogaine. The results are provided below. All parameters were linear and no clinically relevant adverse effects were observed in the trial.

[0055] The subject mean serum levels over time of noribogaine free base from a single dose of 3 mg noribogaine free base under fasting conditions were plotted. The mean C_{max} of 5.2 ng/ml was observed 1.9 hours after administration, while the mean AUC/24 hr of 3.1 ng/ml was obtained.

[0056] The subject mean serum levels over time of noribogaine free base from a single dose of 10 mg noribogaine free base under fasting conditions were plotted. The mean C_{max} of 14.5 ng/ml was observed 2.9 hours after administration, while the mean AUC/24 hr of 10.6 ng/ml was obtained.

[0057] The subject mean serum levels over time of noribogaine free base from a single dose of 30 mg noribogaine free base under fasting conditions were plotted. The mean C_{max} of 55.9 ng/ml was observed between 1.75 hours after administration, while the mean AUC/24 of 29.2 ng/ml was obtained.

[0058] The subject mean serum levels over time of noribogaine free base from a single dose of 60 mg noribogaine free base under fasting conditions were plotted. The mean C_{max} of 116 ng/ml was observed between 1.75 hours after administration, while the mean AUC/24 ng/ml of 61 was obtained.

[0059] The subject mean serum levels over time of noribogaine free base for all 4 cohorts were plotted. The extrapolated dosage of noribogaine free base required to provide a C_{max}

ranging from about 5.2 ng/ml to about 1980 ng/ml and an AUC/24 hr of about 3.1 ng/ml to about 1100 ng/ml was determined.

Example 7

Pharmacokinetics and pharmacodynamics of noribogaine in humans

[0060] Thirty-six healthy, drug-free male volunteers, aged between 18-55 years, were enrolled in and completed the study. This was an ascending single-dose, placebo-controlled, randomised double blind, parallel group study. Mean (SD) age was 22.0 (3.3) years, mean (SD) height was 1.82 (0.08) m, and mean (SD) weight was 78.0 (9.2) kg. Twenty-six subjects were Caucasian, 3 were Asian, 1 Maori, 1 Pacific Islander, and 5 Other. The protocol for this study was approved by the Lower South Regional Ethics Committee (LRS/12/06/015), and the study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12612000821897). All subjects provided signed informed consent prior to enrolment, and were assessed as suitable to participate based on review of medical history, physical examination, safety laboratory tests, vital signs and ECG.

[0061] Within each dose level, 6 participants were randomized to receive noribogaine and 3 to receive placebo, based on a computer-generated random code. Dosing began with the lowest noribogaine dose, and subsequent cohorts received the next highest dose after the safety, tolerability, and blinded pharmacokinetics of the completed cohort were reviewed and dose-escalation approved by an independent Data Safety Monitoring Board. Blinded study drug was administered as a capsule with 240 ml of water after an overnight fast of at least 10 hours. Participants did not receive any food until at least 5 hours post-dose. Participants were confined to the study site from 12 hours prior to drug administration, until 72 hours post-dose, and there were subsequent outpatient assessments until 216 hours post-dose.

[0062] Blood was obtained for pharmacokinetic assessments pre-dose and then at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 18, 24, 30, 36, 48, 60, 72, 96, 120, 168 and 216 hours post-dose. Samples were centrifuged and plasma stored at -70 °C until analyzed. Block 24 hour urine collections were obtained following study drug administration for the 30 and 60 mg cohorts. Aliquots were frozen at -20 °C until analyzed.

[0063] Pulse oximetry and capnography data were collected continuously using a GE Carescape B650 monitoring system from 2 hours prior to dosing and until six hours after dosing, and thereafter at 12, 24, 48 and 72 hours post-dosing. Additional oximetry data were

collected at 120, 168 and 216 hours. Pupillary miosis was assessed by pupillometry. Dark-adapted pupil diameter was measured in triplicate using a Neuroptics PLR-200 pupillometer under standardized light intensity (<5 lux) pre-dose, and at 2, 4, 6, 12, 24, 48, 72, 96, 120, 168 and 216 hours post-dosing.

[0064] Plasma noribogaine concentrations were determined in the 3 mg and 10 mg dose groups using a validated, sensitive LCMSMS method. Sample preparation involved double extraction of basified plasma samples with tert-butyl methyl ether, drying the samples under a stream of nitrogen and reconstitution of sample with acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5µm C18 column and detected with a triple – quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d₄ was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 → 122.3, and for the internal standard noribogaine-d₄ m/z 301.1 → 122.2. Analyst[®] software was used for data acquisition and processing. The ratio of the peak area of noribogaine to the internal standard noribogaine-d₄ was used for calibration and measurement of the unknown concentration of noribogaine. The lower limit of quantification (LLOQ) was 0.025 ng/ml noribogaine. The calibration curve was between 0.025 and 25.600 ng/ml noribogaine. Mobile phase A was acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid, and mobile phase B was acetonitrile:B.P. water (95:5, v/v) containing 0.1% (v/v) formic acid. Total run time was 6 minutes. Binary flow: Initial concentration was 8% mobile phase B; hold at 8% mobile phase B for 0.5 minutes and linear rise to 90% mobile phase B over 1.5 minutes; hold at 90% mobile phase B for 1 minute and then drop back to 8% mobile phase B over 0.01 minute. Equilibrate system for 3 minutes. Total run time was 6 minutes. Within- and between-day assay precision was < 9%, and within- and between-day assay accuracy was < 9%.

[0065] Plasma noribogaine concentrations were determined in the 30 mg and 60 mg dose groups using a validated, sensitive LCMSMS method. Sample preparation involved deproteinization of plasma samples with acetonitrile and dilution of sample with 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5µm C18 column and detected with a triple – quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d₄ was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 → 122.3, and for the internal standard noribogaine-d₄ m/z 301.1 → 122.2. Analyst[®] software

was used for data acquisition and processing. The ratio of the peak area of noribogaine to the internal standard noribogaine-d₄ was used for calibration and measurement of the unknown concentration of noribogaine. The LLOQ was 0.50 ng/ml noribogaine. The calibration curve was between 0.50 and 256.00 ng/ml noribogaine. Mobile phase was the same as method A, and binary flow was also the same as method A. The within- and between-day assay precision was < 9%, and the within- and between-day assay accuracy was < 9%.

[0066] Plasma noribogaine glucuronide concentrations were determined in the 30 mg and 60 mg dose groups using a validated sensitive LCMSMS method. Sample preparation involved deproteinization of plasma samples with acetonitrile, drying the samples under a stream of nitrogen and reconstitution of sample with acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5µm C18 column and detected with a triple – quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d₄ was used as the internal standard. The precursor-product ion transition values for noribogaine glucuronide were m/z 472.8 → 297.3, and for the internal standard noribogaine-d₄ m/z 301.1 → 122.2. Analyst[®] software was used for data acquisition and processing. The ratio of the peak area of noribogaine glucuronide to the internal standard noribogaine-d₄ was used for calibration and measurement of the unknown concentration of noribogaine glucuronide. The LLOQ was 0.050 ng/ml noribogaine glucuronide. The calibration curve was between 0.050 and 6.400 ng/ml noribogaine glucuronide. Mobile phases was the same as method A. Binary flow: Initial concentration was 6% mobile phase B; hold at 6% mobile phase B for 0.5 minutes and linear rise to 90% mobile phase B over 2 minutes; hold at 90% mobile phase B for 1 minute and then drop back to 6% mobile phase B over 0.01 minute. Equilibrate system for 3.5 minutes. Total run time was 7 minutes. The within- and between-day assay precision was < 11%, and the within- and between-day assay accuracy was < 10%.

[0067] Urine noribogaine and noribogaine glucuronide concentrations were determined in the 30 mg and 60 mg dose groups using a validated sensitive LCMSMS method. Sample preparation involved deproteinization of urine samples with acetonitrile and dilution of the sample with 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5µm C18 column and detected with a triple – quadrupole API 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d₄ was used as the internal standard. The precursor-product ion transition values for noribogaine

were m/z 297.6 $\rightarrow$ 122.3, noribogaine glucuronide m/z 472.8 $\rightarrow$ 297.3, and for the internal standard noribogaine- d_4 m/z 301.1 $\rightarrow$ 122.2. Analyst[®] software was used for data acquisition and processing. The ratios of the peak area of noribogaine and noribogaine glucuronide to the internal standard noribogaine- d_4 were used for calibration and measurement of the unknown concentration of noribogaine and its glucuronide. Assay LLOQ was 20.0 ng/ml for noribogaine and 2.0 ng/ml for noribogaine glucuronide. The calibration curve was between 20.0 and 5120.0 ng/ml noribogaine, and 2.0 and 512.0 ng/ml noribogaine glucuronide. Mobile phases were as described in method A, and binary flow as in method C. The within- and between-day assay precision was $< 13\%$, and within- and between-day assay accuracy was $< 12\%$.

[0068] Noribogaine and noribogaine glucuronide concentrations above the limit of quantification were used to calculate pharmacokinetic parameters using model-independent methods. The maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were the observed values. Plasma concentration data in the post-distribution phase of the plasma concentration-time plot were fitted using linear regression to the formula $\ln C = \ln C_0 - t \cdot K_{el}$, where C_0 was the zero-time intercept of the extrapolated terminal phase and K_{el} was the terminal elimination rate constant. The half-life ($t_{1/2}$) was determined using the formula $t_{1/2} = 0.693/K_{el}$. The area under the concentration-time curve (AUC) from time zero to the last determined concentration-time point (t_f) in the post distribution phase was calculated using the trapezoidal rule. The area under the curve from the last concentration-time point in the post distribution phase (C_{tf}) to time infinity was calculated from $AUC_{t-\infty} = C_{tf}/K_{el}$. The concentration used for C_{tf} was the last determined value above the LLOQ at the time point. The total $AUC_{0-\infty}$ was obtained by adding AUC_{tf} and $AUC_{t-\infty}$. Noribogaine apparent clearance (CL/F) was determined using the formula $CL/F = \text{Dose}/AUC_{0-\infty} \times 1000$, and apparent volume of distribution (V_d/F) was determined using the formula $V_d/F = (CL/F)/K_{el}$. Total urine noribogaine was the sum of both analytes.

[0069] Summary statistics (means, standard deviations, and coefficients of variation) were determined for each dose group for safety laboratory test data, ECG and pharmacokinetic parameters, and pharmacodynamic variables. Categorical variables were analysed using counts and percentages. Dose-proportionality of AUC and C_{max} was assessed using linear regression. The effect of dose on pharmacodynamic parameter values over time was assessed using two-factor analysis of variance (ANOVA). Pairwise comparisons (with Tukey-Kramer

adjustment) between each dose group to the placebo were conducted at each time point using the least squares estimates obtained from the ANOVA, using SAS Proc Mixed (SAS ver 6.0).

Results

[0070] Pharmacokinetics: Mean plasma concentration-time plots of noribogaine are shown in Figure 1, and mean pharmacokinetic parameters are shown in Table 6.

Table 6

Noribogaine	3 mg (n=6) (mean (SD))	10 mg (n=6) (mean (SD))	30 mg (n=6) (mean (SD))	60 mg (n=6) (mean (SD))
AUC _{0-∞} (ng.hr/ml)	74.2 (13.1)	254.5 (78.9)	700.4 (223.3)	1962.2 (726.5)
AUC ₀₋₂₁₆ (ng.hr/ml)	72.2 (13.2)	251.4 (78.5)	677.6 (221.1)	1935.4 (725.4)
C _{max} (ng/ml)	5.2 (1.4)	14.5 (2.1)	55.9 (14.8)	116.0 (22.5)
T _{max} (hr)	1.9 (0.6)	2.9 (1.8)	1.8 (0.6)	2.4 (0.6)
t _{1/2} (hr)	40.9 (8.7)	49.2 (11.5)	27.6 (7.0)	29.1 (9.3)
Vd/F (L)	2485.1 (801.5)	3085.8 (1197.0)	1850.8 (707.9)	1416.8 (670.1)
CL/F (L/h)	41.4 (7.0)	42.3 (12.0)	46.9 (16.4)	34.0 (11.4)
Noribogaine glucuronide				
AUC _{0-∞} (ng.hr/ml)	-	-	25.8 (9.3)	67.1 (21.9)
AUC ₀₋₂₁₆ (ng.hr/ml)	-	-	25.7 (9.1)	65.0 (21.5)
C _{max} (ng/ml)	-	-	1.8 (0.6)	4.1 (1.2)
T _{max} (hr)	-	-	3.0 (0.6)	3.8 (1.2)
t _{1/2} (hr)	-	-	20.6 (4.9)	23.1 (3.0)

[0071] Noribogaine was rapidly absorbed, with peak concentrations occurring 2-3 hours after oral dosing. Fluctuations in individual distribution-phase concentration-time profiles may suggest the possibility of enterohepatic recirculation (see highlighted individual 4-8 hour profiles in Figure 1, insert). Both C_{max} and AUC increased linearly with dose (Table 6, upper panel). Mean half-life estimates of 28-50 hours were observed across dose groups for noribogaine. Volume of distribution was extensive (1417-3086 L across dose groups).

[0072] Mean plasma noribogaine glucuronide concentration-time plots for the 30 mg and 60 mg dose group are shown in Figure 2, and mean pharmacokinetic parameters are shown in Table 6, lower panel. Noribogaine glucuronide was detected in all subjects by 0.75 hours, with peak concentrations occurring 3-4 hours after noribogaine dosing. Mean half-life of 21-

23 hours was estimated for plasma noribogaine glucuronide. The proportion of noribogaine glucuronide C_{max} and AUC relative to noribogaine was 3-4% for both dose groups. Total urine noribogaine elimination was 1.16 mg and 0.82 mg for the 30 mg and 60 mg dose groups respectively, representing 3.9% and 1.4% of the doses administered.

[0073] Pharmacodynamics: There was no evidence of pupillary constriction in subjects dosed with noribogaine. No between-dose group differences in pupil diameter were detected over time. After adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences ($p>0.9$).

[0074] Noribogaine treatment showed no analgesic effect in the cold pressor test. Analgesic effect was assessed based on duration of hand immersion in ice water and on visual analog scale (VAS) pain scores upon hand removal from the water bath. For duration of hand immersion, after adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences ($p>0.9$). Similarly, for VAS pain scores, after adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences ($p=0.17$).

Example 8

Safety and tolerability of noribogaine in humans

[0075] Safety and tolerability of noribogaine were tested in the group of volunteers from Example 1. Cold pressor testing was conducted in 1 °C water according to the method of Mitchell et al. (*J Pain* 5:233-237, 2004) pre-dose, 6, 24, 48, 72 and 216 hours post-dosing. Safety evaluations included clinical monitoring, recording of adverse events (AEs), safety laboratory tests, vital signs, ECG telemetry from -2h to 6h after dosing, and 12-lead electrocardiograms (ECGs) up to 216 hours post-dosing.

Results

[0076] A total of thirteen adverse events were reported by seven participants (Table 7). Six adverse events were reported by three participants in the placebo group, five adverse events were reported by two subjects in the 3 mg dose group, and one adverse event was reported by single subjects in the 10 mg and 30 mg dose groups, respectively. The most common adverse events were headache (four reports) and epistaxis (two reports). All adverse events were of mild-moderate intensity, and all resolved prior to study completion. There were no changes in vital signs or safety laboratory tests of note. In particular, there were no changes in oximetry or capnography, or changes in respiratory rate. There were no QTcF values >500 msec at any

time. One subject dosed with 10 mg noribogaine had a single increase in QTcF of >60 msec at 24 hours post-dosing.

Table 7

Dose (mg)	Mild	Moderate	Severe
Placebo	Blepharitis Bruising Dry Skin Eye pain, nonspecific Infection at cannula site	Epistaxis	-
3	Back pain Dizziness Epistaxis Headache	Headache	-
10	Headache	-	-
30	Headache	-	-
60	-	-	-

EXAMPLE 9

Efficacy of noribogaine in humans

[0077] The efficacy of noribogaine in humans was evaluated in opioid-dependent participants in a randomized, placebo-controlled, double-blind trial. In the first cohort, six patients were orally administered a single dose of 60 mg noribogaine, and three patients received placebo. In the second cohort, five patients were orally administered a single dose of 120 mg noribogaine, and three patients received placebo. Treatment was administered 2 hours after last morphine dose and the time to resumption of morphine (opioid substitution treatment, OST) was determined. No adverse effects of noribogaine were observed in any of the participants, including no hallucinatory effects.

[0078] Figure 3 indicates the serum noribogaine concentration over time. Serum concentrations for 120 mg dose (black squares) are estimated based on data from the 60 mg dose (gray diamonds).

Blinded Results

[0079] Patients in the first cohort exhibited an average time to resumption of opioids after treatment with 60 mg noribogaine or placebo of approximately 8.7 hours, which is almost 2

hours longer than that reported for untreated patients in a similar study. Patients in the second cohort exhibited an average time to resumption of opioids after treatment with 120 mg noribogaine or placebo of approximately 23 hours. Figure 4A indicates the average time to resumption of morphine for control (untreated, light gray bar), first cohort (dark gray bar) and second cohort (black bar). Mean prolongation of the QT interval was less than 10 ms for patients in the first cohort and was less than 40 ms in the second cohort.

[0080] Figure 4B indicates the estimated noribogaine concentration (based on the data from Figure 3) at the time of resumption of morphine for each patient.

[0081] Although the study was blinded, the patients in the second cohort who received placebo were construed to be those patients exhibiting no prolongation of the QT interval. The average time to resumption of OST for the remaining five patients was determined to be approximately 26.8 hours, as indicated in Figure 5A (black bar). Figure 5B indicates the estimated noribogaine concentration (based on the data from Figure 3) at the time of resumption of morphine for each (presumed) noribogaine-treated patient.

What is claimed is:

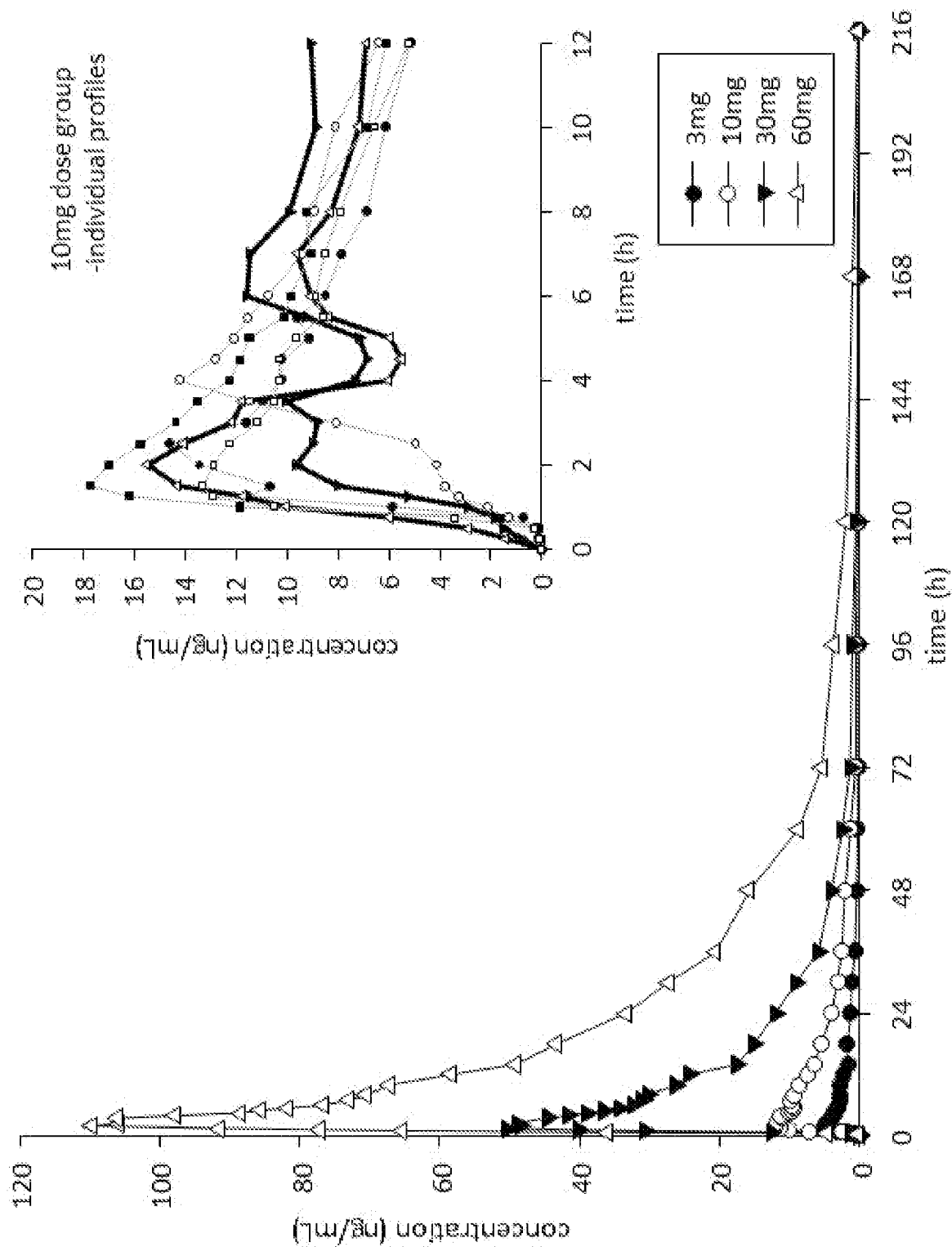
1. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1980 ng/mg serum and an average AUC/24 hr of about 1,100 ng/ml.
2. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1800 ng/mg serum and an AUC/24 hr of about 1000 ng/ml.
3. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1620 ng/mg serum and an AUC/24 hr of about 900 ng/ml.
4. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1440 ng/mg serum and an AUC/24 hr of about 800 ng/ml.
5. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1260 ng/mg serum and an AUC/24 hr of about 700 ng/ml.
6. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 1400 ng/mg serum and an AUC/24 hr of from about 600 ng/ml.
7. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a $C_{\max}$ of noribogaine of less than about 900 ng/mg serum and an AUC/24 hr of about 500 ng/ml.

8. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 720 ng/mg serum and an AUC/24 hr of about 400 ng/ml.
9. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 540 ng/mg serum and an AUC/24 hr of about 300 ng/ml.
10. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 360 ng/mg serum and an AUC/24 hr of about 200 ng/ml.
11. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine that provides a C_{max} of noribogaine of less than about 180 ng/mg serum and an AUC/24 hr of about 100 ng/ml.
12. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 100 mg to about 600 mg at intervals of about 24 hours.
13. The method according to claim 12, wherein the patient is administered a dosage of noribogaine from about 100 mg to about 500 mg at intervals of about 24 hours.
14. The method according to claim 12, wherein the patient is administered a dosage of noribogaine from about 100 mg to about 400 mg at intervals of about 24 hours.
15. The method according to claim 12, wherein the patient is administered a dosage of noribogaine from about 100 mg to about 300 mg at intervals of about 24 hours.
16. The method according to claim 12, wherein the patient is administered a dosage of noribogaine from about 100 mg to about 200 mg at intervals of about 24 hours.

17. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 200 mg to about 600 mg at intervals of about 24 hours.
18. The method according to claim 17, wherein the patient is administered a dosage of noribogaine from about 200 mg to about 500 mg at intervals of about 24 hours.
19. The method according to claim 17, wherein the patient is administered a dosage of noribogaine from about 200 mg to about 400 mg at intervals of about 24 hours.
20. The method according to claim 17, wherein the patient is administered a dosage of noribogaine from about 200 mg to about 300 mg at intervals of about 24 hours.
21. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 300 mg to about 600 mg at intervals of about 24 hours.
22. The method according to claim 21, wherein the patient is administered a dosage of noribogaine from about 300 mg to about 500 mg at intervals of about 24 hours.
23. The method according to claim 21, wherein the patient is administered a dosage of noribogaine from about 300 mg to about 400 mg at intervals of about 24 hours. In some embodiments each patient is administered from about 400 mg to about 500 mg at intervals of about 24 hours.
24. A method for treating withdrawal symptoms in a patient suffering from withdrawal from addiction to a substance comprising administering to the patient a dosage of noribogaine from about 500 mg to about 600 mg at intervals of about 24 hours.

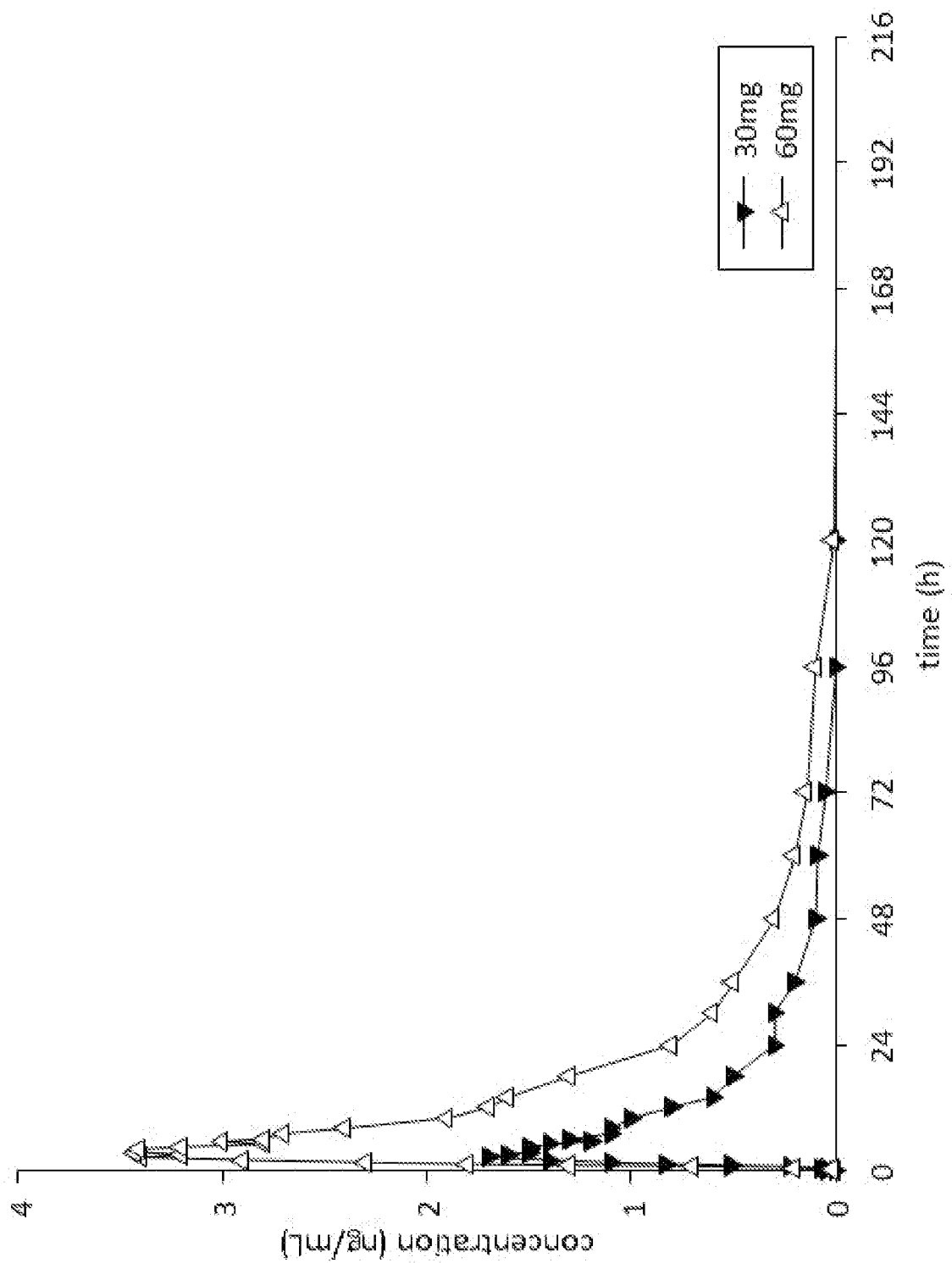
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FIGURE 1



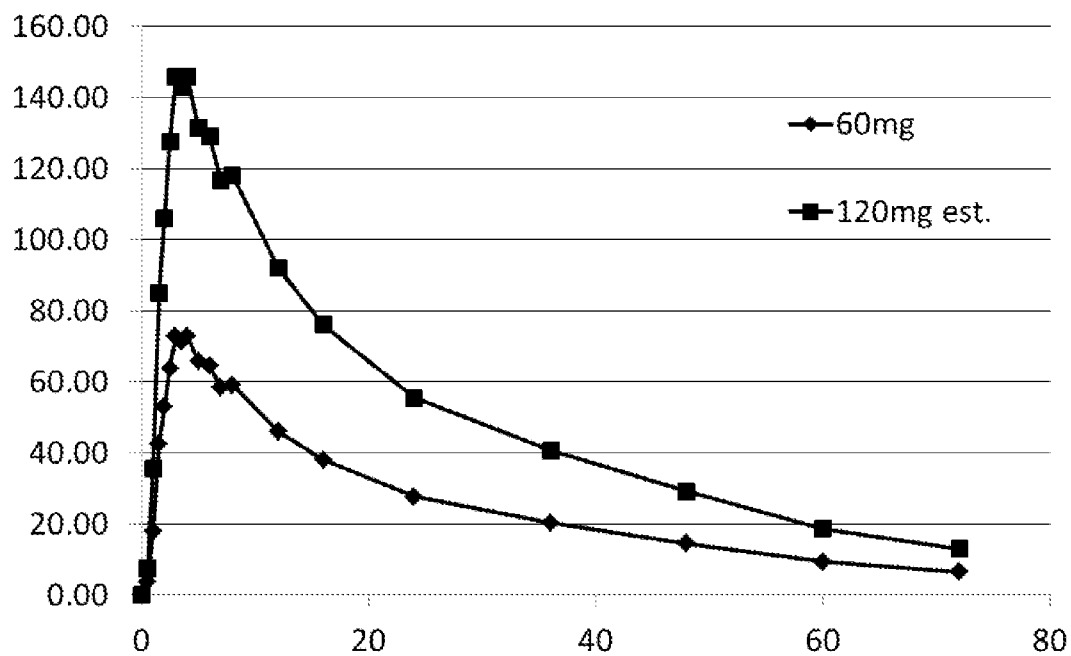
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FIGURE 2

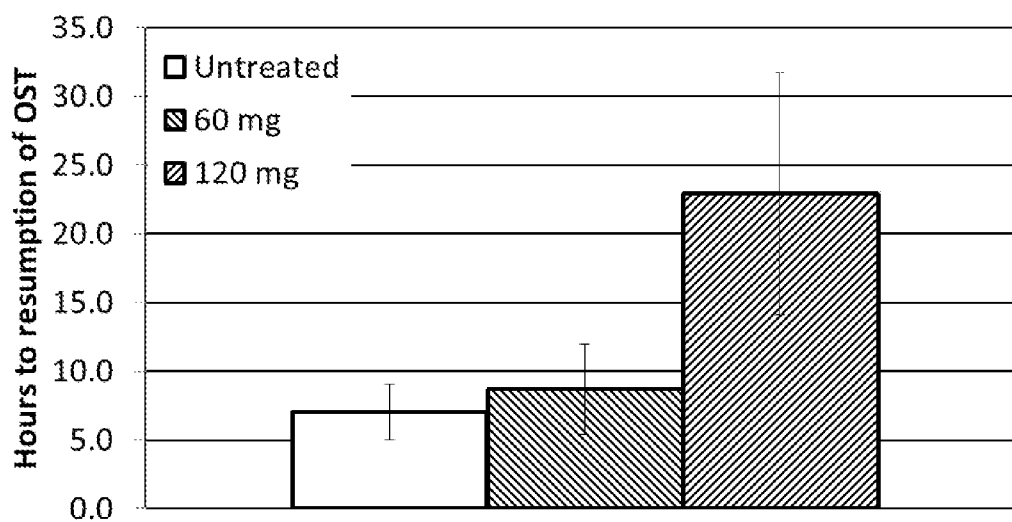
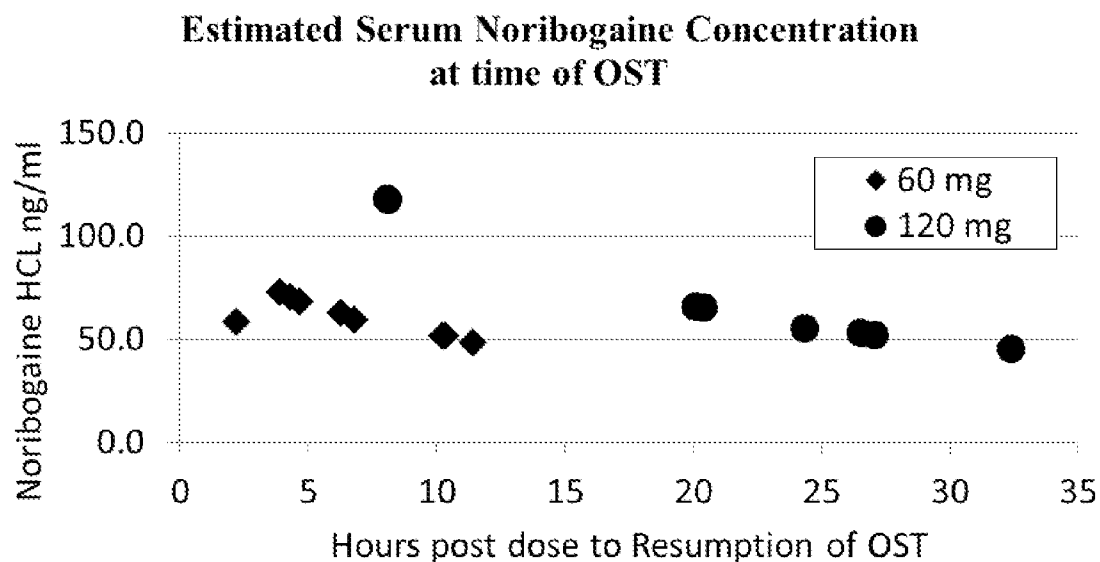


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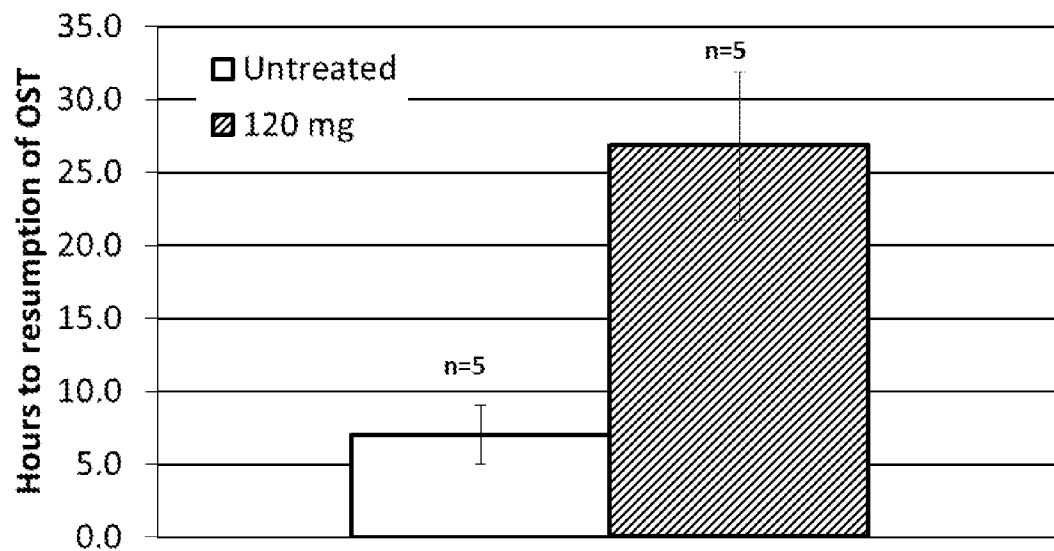
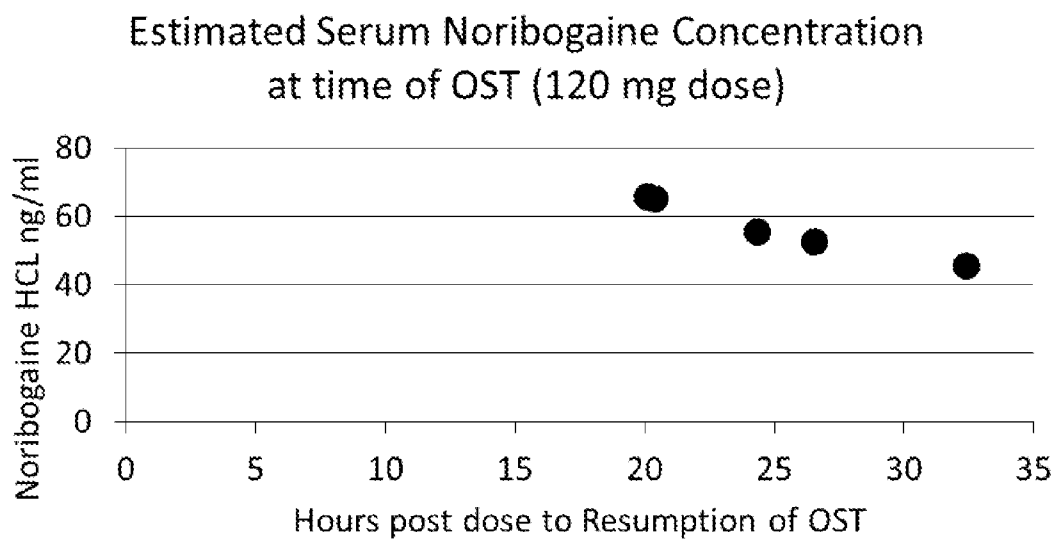
FIGURE 3



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FIGURE 4A**FIGURE 4B**

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FIGURE 5A**FIGURE 5B**

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT
(PCT Article 17(2)(a), Rules 13ter.1(c) and (d) and 39)

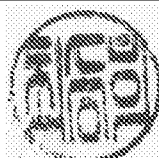
Applicant's or agent's file reference 364105-2560	IMPORTANT DECLARATION	Date of mailing (<i>day/month/year</i>) 28 July 2014 (28.07.2014)
International application No. PCT/US2014/028946	International filing date (<i>day/month/year</i>) 14 March 2014 (14.03.2014)	(Earliest) Priority date (<i>day/month/year</i>) 15 March 2013 (15.03.2013)
International Patent Classification (IPC) or both national classification and IPC A61K 31/55(2006.01)i, A61P 25/30(2006.01)i, A61P 25/00(2006.01)i		
Applicant DEMEX, INC.		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. ☒ The subject matter of the international application relates to:
 - a. ☐ scientific theories
 - b. ☐ mathematical theories
 - c. ☐ plant varieties
 - d. ☐ animal varieties
 - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes
 - f. ☐ schemes, rules or methods of doing business
 - g. ☐ schemes, rules or methods of performing purely mental acts
 - h. ☐ schemes, rules or methods of playing games
 - i. ☒ methods for treatment of the human body by surgery or therapy
 - j. ☐ methods for treatment of the animal body by surgery or therapy
 - k. ☐ diagnostic methods practised on the human or animal body
 - l. ☐ mere presentation of information
 - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art
2. ☐ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

☐ the description
 ☐ the claims
 ☐ the drawings
3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).
4. Further comments:

Name and mailing address of ISA/KR  International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea Facsimile No. +82-42-472-7140	Authorized officer CHOI, Sung Hee Telephone No. +82-42-481-8740	
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