CLINICAL STUDY PROTOCOL

DemeRx NB Protocol Number: **DMX-NB-001**
Richmond Pharmacology Study Number: **C23026**

Title:	A randomized, double-blind, placebo-controlled trial to evaluate multiple dose pharmacokinetics, pharmacodynamics, safety, and tolerability of ascending doses of noribogaine in healthy volunteers.
Brief Title:	Multiple Ascending Dose Noribogaine PK/PD in healthy volunteers
Phase:	Phase 1
Investigational Product:	Noribogaine Capsules
IRAS ID:	1009536
EudraCT Number:	2024-000121-41
Sponsor:	DemeRx NB, Inc. 1951 NW 7th Avenue Miami, Florida, USA
Principal Investigator:	Dr Jorg Taubel MD FFPM FESC Richmond Pharmacology Ltd.
Trial Site:	Richmond Pharmacology Ltd. 1a Newcomen Street, London Bridge, London SE1 1YR, UK Telephone: +44 (0)20 7042 5800 Fax: +44 (0)20 7378 9135
Protocol Version and Date:	Version 6.0 20 Nov 2024

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the trial, without written authorisation from DemeRx NB, Inc. or its affiliates.

TRIAL SYNOPSIS

Sponsor:	**Protocol Number:**
DemeRx NB, Inc.	DMX-NB-001
Name of Investigational Product:	**Phase of Development:**
Noribogaine (as noribogaine hydrochloride) Capsules	Phase 1 (Healthy Volunteers)

Protocol Title: A randomized, double-blind, placebo-controlled trial to evaluate multiple dose pharmacokinetics, pharmacodynamics, safety, and tolerability of ascending doses of noribogaine in healthy adult volunteers.

Brief Title: Multiple Ascending Dose Noribogaine PK/PD in healthy volunteers

Trial Objectives:

The primary objectives are to determine the pharmacokinetics of noribogaine capsules and to establish a PK/PD relationship of noribogaine concentration on change in QT/QTcI interval.

A secondary objective of this trial is to evaluate the safety and tolerability of noribogaine.

Pharmacokinetic Endpoints:

Maximum plasma concentration (C_{max}: Day 1 & Day 8), time to maximum plasma concentration (T_{max}: Day 1 & Day 8), trough concentration prior to next dose (C_{12}, C_{24}), area under the curve at 12 hours and 24 hours ($AUC_{0\text{-}12\ hours}$, $AUC_{0\text{-}24\ hours}$: Day 1 & Day 8, and to infinity ($AUC_{0\text{-}infinity}$), accumulation ratio for AUC, accumulation ratio C_{max} -life ($t_{½}$), clearance (CL/F) and volume of distribution (Vz/F), whole blood to plasma ratio (1 hour, 2 hours and 6 hours), amount excreted (Ae) (Day 1 & Day 8) and cumulative amount excreted (Cum Ae) (Day 1 & Day 8).

Pharmacodynamic Endpoints:

QT interval corrected for heart rate using individual specific QT interval correction (QTcI) measures (Day 1 & Day 8).

Concentration-QTc relationship assessed on placebo-
(Day 1 & Day 8).

Safety Endpoints:

Adverse events will be elicited by asking the participants (prior to any trial y rating scales). Any events spontaneously reported by the participant or observed by Investigator staff (physical examinations) will be recorded. Vital signs, clinical laboratory results and ECG abnormalities will be reported as an adverse event if considered clinically significant.

Trial Design:

Randomised, double-blind, sequential-group, multiple-dose, placebo-controlled, dose escalation trial to characterize the pharmacokinetics (PK), pharmacodynamics (PD) and safety of noribogaine, in up to 60 healthy volunteers. Participants will be assigned to one of the four possible cohorts. Each participant will receive noribogaine capsules or placebo twice daily for 8 days (except Day 8, morning only).

Cohort 1: 20 mg per day (One 10 mg capsule or placebo twice daily)

Cohort 2: 40 mg per day (One 20 mg capsule or placebo twice daily)

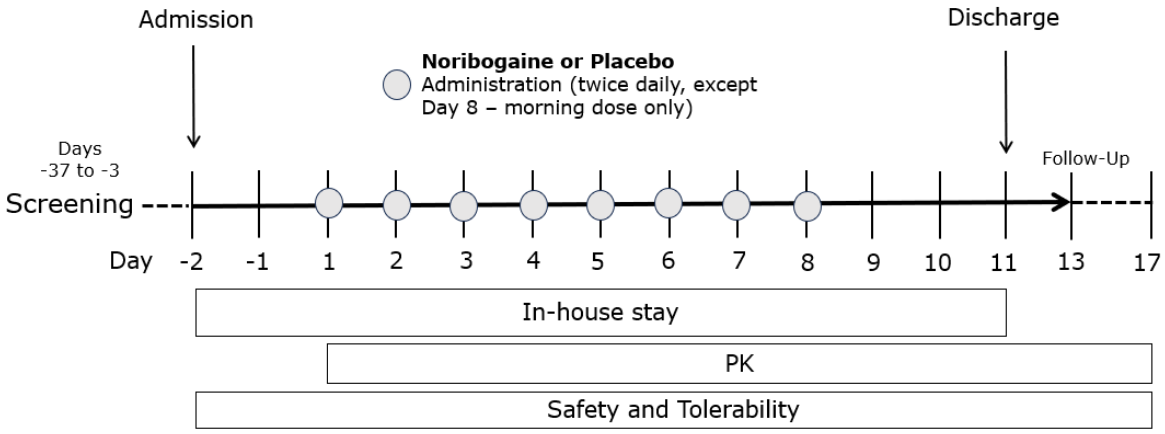
Cohort 3: 60 mg per day (One 10 mg capsule & one 20 mg capsule or placebo twice daily)

Cohort 4: 80 mg per day (Two 20 mg capsules or placebo twice daily)

The trial consists of three phases: Screening, Treatment Period and Follow-up. Screening can occur up to 35 days before Admission, participants will then stay in the inpatient facility for 13 days to complete the treatment phase of the trial and will be discharged following completion of the discharge procedures at the end of the period. Participants will return to the facility 2 to 6 days after Discharge for the follow-up procedures.

All participants who have given their written informed consent will be screened for eligibility during the Screening window from Day -37 to Day -3 to participate in the trial as per the Schedule of Assessments. Participants must meet all the inclusion criteria and none of the exclusion criteria to be randomised in this protocol.

Trial Flow Chart



Safety Review:

Safety review pre-defined stopping criteria in relation to QTc prolongation and cardiac safety.

Safety Review Committee (SRC)

Safety review will be conducted after at least 8 subjects have completed each dose cohort. Data will be reviewed after completion of each dose cohort by the SRC, to determine progression to the next cohort, in accordance with the SRC Charter.

Data Review

Data review will include clinical laboratory test results, safety ECG, vital signs and adverse events.

Planned Sample Size:

60 participants

4 dose groups with 15 participants per group (12 will be randomised to noribogaine and 3 will be randomised to placebo).

Main Criteria for Inclusion:

Healthy male and female participants between the ages of 18 to 45 inclusive, with BMI 18 - 30 kg/m^2 with normal ECG [illegible] accurate assessment of the QT interval. Participants must agree to use highly effective methods of contraception.

Investigational Product(s), Route of Administration and Dosage:

Noribogaine 10 mg Capsule

Noribogaine 20 mg Capsule

Placebo Capsule

Oral route

Cohort 1: 20 mg per day (One 10 mg capsule or placebo twice daily)

Cohort 2: 40 mg per day (One 20 mg capsule or placebo twice daily)

Cohort 3: 60 mg per day (One 10mg capsule & one 20 mg capsule or placebo twice daily)

Cohort 4: 80 mg per day (Two 20 mg capsules or placebo twice daily)

Treatment Duration:

Screening can occur up to 35 days before Admission. The inpatient stay is 13 days, during which the treatment will be administered. Treatment will be administered for 8 days, with the participants returning to the trial site 2 to 6 days after discharge for follow-up procedures. The total participant duration is up to 54 days to complete the entire trial.

Statistical Analyses:

Sample Size Justification

[illegible] dose response in QTc was observed across the expected range of doses and exposures. Using results from a simulation based on data from a prior trial in healthy volunteers, the probability is 95% that a sample size of 12 participants will produce a two-sided 95% confidence interval with a distance from the mean to the limits that is less than or equal to 0.2 if the population standard deviation is estimated to be no more than 0.2 on the natural log scale. This corresponds to a calculated geometric mean of approximately 80 ng/ml with an upper bound of the 95% confidence interval being less than or equal to 100 ng/ml. The standard deviation is expected to be less than or equal to 20 ng/ml.

1. INTRODUCTION

1.1. Background

Noribogaine is being developed as a treatment for alcohol use disorder based on accumulated knowledge of the pharmacology and toxicology of noribogaine which has been shown to have efficacy in animal models of alcohol addiction [1],[2],[3],[4].

Alcohol addiction encompasses the dysregulation of multiple central nervous system pathways involved in executive function leading to excessive consumption of alcohol, despite negative health and social consequences, and withdrawal symptoms when access to alcohol is prevented [5]. Ethanol exerts its toxicity through changes to multiple neurotransmitter systems, including serotonin, dopamine, gamma-aminobutyric acid, glutamate, acetylcholine, and opioid systems. These neurotransmitter imbalances result in dysregulation of brain circuits responsible for reward, motivation, decision making, affect, and the stress response.

Previous clinical trials have tested single and multiple doses of noribogaine in healthy individuals and opioid-dependent patients. In healthy subjects (Study ZPS-468, ACTRN1261000821897), doses from 3 to 60 mg were well tolerated with minor adverse events such as headaches and nosebleeds. Opioid-dependent patients (Studies ZPS-513, ACTRN12613001064796; DMX-100, UTN U1111-1159-4757) received higher doses (60 - 180 mg) and reported adverse events including nausea, headache, and anxiety. These could be related to opioid withdrawal or noribogaine itself. Importantly, no serious adverse reactions were observed in any trial.

Single oral administration of noribogaine shows that the drug reaches peak levels in the bloodstream within 2 - 4 hours depending on the dose, with a half-life of 24 - 50 hours. The dose and its effect on blood levels increased proportionally in healthy subjects (Studies ZPS-468). An increase in the QT interval on electrocardiograms was observed in all studies, which warrants further investigation, especially considering the presence of opioids in some studies.

Overall, these trials suggest that noribogaine can be safely administered orally at various doses and has the potential for long-acting effects in addiction treatment.

2. TRIAL OBJECTIVES AND OUTCOMES

Primary	
Objective	**Endpoint**
To determine the pharmacokinetics of noribogaine capsules.	Maximum plasma concentration (C_{max}: Day 1 & Day 8), time to maximum plasma concentration (T_{max}: Day 1 & Day 8), trough concentration prior to next dose (C_{12}, C_{24}), area under the curve at 12 hours and 24 hours ($AUC_{0\text{-}12\ hours}$, $AUC_{0\text{-}24\ hours}$: Day 1 & Day 8, and to infinity ($AUC_{0\text{-}infinity}$), accumulation ratio for AUC, accumulation ratio C_{max}, terminal [illegible] -life ($t_{½}$), clearance (CL/F) and volume of distribution (Vz/F), whole blood to plasma ratio (1 hour, 2 hours and 6 hours), amount excreted (Ae) (Day 1 & Day 8) and cumulative amount excreted (Cum Ae) (Day 1 & Day 8).

To establish a PK/PD relationship of noribogaine concentration on change in QT/QTcI interval.	QT interval corrected for heart rate using individual specific QT interval correction (QTcI) measures (Day 1 & Day 8). Concentration-QTc relationship assessed on placebo-adjusted change from baseline for QTcI (ΔΔQTcI) (Day 1 and Day 8).
Secondary	
To evaluate the safety and tolerability of noribogaine.	Adverse events will be elicited by a verbal probe (prior to any trial rating scales). Any events spontaneously reported by the participant or observed by Investigator's staff (physical examinations) will be recorded. Vital signs, clinical laboratory results and ECG abnormalities will be reported as an adverse event if considered clinically significant.

Schedule of Assessments

Trial visit	**Screening**	**Admission**	**Treatment Period**											**Discharge or Early Termination**	**Follow-Up**
Day	**-37 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**15 (+/- 2 days)**
Informed Consent[a]	X														
Eligibility (Inclusion/Exclusion Criteria)	X	X	X												
Demographics	X														
Medical History and Current Medications	X	X[b]													
Smoking History reporting	X														
Urine Drug Screen	X	X													X
Urine Cotinine Screen	X	X													X
HIV, Hepatitis B and C	X														
FSH Testing[c]	X														
-HCG Testing[d]	X	X													X
Postural Assessment of Heart Rate and Blood Pressure[n]	X		X	X			X				X		X		
Exercise Stress Test	X														
Non-residential Visit	X														X
Check-in		X													
Study Residency		X	X	X	X	X	X	X	X	X	X	X	X	X	
Check-out														X	
Randomisation				X											
IMP Administration[e]				X	X	X	X	X	X	X	X				
Meals[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	

Trial visit	**Screening**	**Admission**	**Treatment Period**											**Discharge or Early Termination**	**Follow-Up**
Day	**-37 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**15 (+/- 2 days)**
Safety and Tolerability:															
AE Recording/ Concomitant Medications	→														
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG Triplicate[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Holter	X														
Telemetry[i]			X	X	X	X	X	X	X	X	X				
Height, and BMI	X	X													
Body Weight	X	X													
Physical Examination	X	X												X	
Biochemistry/Coagulation/ Haematology	X	X		X[j]			X[j]							X	X
Urinalysis	X	X		X			X							X	
Serum Potassium, Magnesium & Calcium only[j]					X				X		X				
C-SSRS	X	X												X	
MEQ30				X[k]			X[k]				X[k]				
COVID Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments:															
PK Blood Sampling[l]				X	X	X	X	X	X	X	X	X	X	X	X
PK Urine Sampling				X[m]							X[m]	X[m]	X[m]	X[m]	

AE = adverse event; BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = Follicle Stimulating Hormone; HCG = Human Chorionic Gonadotrophin; HIV = Human Immunodeficiency Virus, IMP = investigational medicinal product; MEQ30 = Mystical Experience Questionnaire; PK = pharmacokinetic.

[a] Written consent prior to the Screening window is permitted.

[b] Update only.

[c] FSH testing is required for post-menopausal women only.

[d] Serum β-HCG testing is required for women of childbearing potential (WOCBP) only.

[e] Participants will be administered noribogaine or placebo capsules at H0 and H12 from D1 to D7 with a final dose on D8 at H0.

[f] Participants will fast for at least 8 hours before the morning dose until at least 4 hours after dosing on all days. Participants will fast for 3 hours before the evening dose until 2 hours after dosing on all days except for Day 1 where they will fast for 3 hours after dosing. Planned D1 meal times will be followed on D-1. For all other doses participants will fast for at least 2 hours before the dose until at least 3 hours after the dose. For non-dosing days, meals will be provided at standard unit times. See **Table 3** for scheduled meal timepoints. Participants will refrain from consuming water from 1 hour pre-dose until 1 hour post-dose. Chilled water is not permitted on Days -1, 1 and 8 due to interference with intensive cardiac assessments.

[g] Respiratory Rate, Oxygen Saturation, Tympanic Temperature, Blood Pressure and Heart Rate. Participants will be supine for a minimum of 5 minutes prior to measurements. See **Table 3** for Treatment Period timepoints.

[h] Participants will be supine for a minimum of 10 minutes prior to measurements. See **Table 3** for Treatment Period timepoints.

[i] 24-hour Holter ECG performed at Screening . Telemetry will be performed from at least H-24 on D-1 to H16 on D8.

[j] Samples to be obtained at H0.

[k] Procedure to be performed at H6.

[l] See **Table 3** for Treatment Period timepoints.

[m] Pooled urine collection will be performed H0 - 6, 6 - 12 and 12 - 24 hours post first dose on Day 1, and at H0 - 6, 6 - 12, 12 - 24, 24 - 36, 36 - 48, and 48 - 72 post last dose on Days 8 - 10. Predose sampling is to be performed within 30 minutes prior to dosing.

[n] At Screening only, postural heart rate and blood pressure will be measured after 3, 5 and 10 minutes of standing from supine position. At D-1, D4, D8 and D10, postural heart rate and blood pressure will be measured after 2 minutes of standing from supine position.

Schedule of Assessments (cont.)

Trial Day	Time (h)	PK Sampling (Plasma)	PK Sampling (Whole Blood)	PK Sampling (Urine)	Vital Signs	Meals	Postural Assessment of Heart Rate and Blood Pressure	12-lead ECG
D-1	-0.5							X
	0				X			X
	1							X
	1.5							X
	2							X
	2.5							X
	3							X
	3.5							X
	4					X		X
	6							X
	7							X
	8					X		X
	10						X	
	11							X
	12							X
	12.5							X
	13							X
	13.5							X
	14							X
	14.5							X
	15					X		X
	16							X
D1	-1				X			
	-0.5							X
	0 (Dose)	X [b]		X [b]	X [b]			X [b]

Trial Day	Time (h)	PK Sampling (Plasma)	PK Sampling (Whole Blood)	PK Sampling (Urine)	Vital Signs	Meals	Postural Assessment of Heart Rate and Blood Pressure	12-lead ECG
	1	X	X	X H0 to H6 collection	X			X
	1.5	X						X
	2	X	X		X			X
	2.5	X						X
	3	X						X
	3.5	X						X
	4	X			X	X		X
	6	X	X	X H6 to H12 collection				X
	7							X
	8	X				X		X
	10						X	
	11							X
	12 (Dose)	X[b]		X H12 to H24 collection	X[b]			X[b]
	12.5							X
	13	X			X			X
	13.5	X						X
	14	X			X			X
	14.5	X						X
	15	X				X		X
	16	X			X			X
D2	-1				X			
	0 (Dose)	X[b]			X[b]			X[b]
	1				X			
	2	X			X			X
	4				X	X		
	8					X		
	12 (Dose)	X[b]			X[b]			X

Trial Day	Time (h)	PK Sampling (Plasma)	PK Sampling (Whole Blood)	PK Sampling (Urine)	Vital Signs	Meals	Postural Assessment of Heart Rate and Blood Pressure	12-lead ECG
	13				X			
	14	X			X	X		X
	16				X			
D3	-1				X			
	0 (Dose)	X [b]			X [b]			X [b]
	1	X			X			X
	1.5	X						X
	2	X			X			X
	2.5	X						X
	3	X						X
	3.5							
	4	X			X	X		X
	6							X
	8					X		X
	12 (Dose)	X [b]			X [b]			X [b]
	13				X			
	14	X			X	X		X
	15							X
	16				X			
D4-D7	-1				X			
	0 (Dose)	X [b]			X [b]			X [b]
	1				X			
	2	X			X			X
	4				X	X		
	7							X
	8					X		
	10						X (Day 4 only)	

Trial Day	Time (h)	PK Sampling (Plasma)	PK Sampling (Whole Blood)	PK Sampling (Urine)	Vital Signs	Meals	Postural Assessment of Heart Rate and Blood Pressure	12-lead ECG
	12 (Dose)	X [b]			X [b]			X [b]
	13				X			
	14	X			X			X
	15					X		
	16				X			
D8	-1							X
	0 (Dose)	X [b]		X [b]	X [b]			X [b]
	1	X		X H0 to H6 collection	X			X
	1.5	X						X
	2	X			X			X
	2.5	X						X
	3	X						X
	3.5	X						X
	4	X			X	X		X
	6	X		X H6 to H12 collection				X
	7							X
	8	X				X		X
	10						X	
	12	X		X H12 to H24 collection				X [b]
	12.5							X
	14	X				X		X
	16	X						X
D9	24	X		X H24 to H36 collection	X	X		X
	30	X						X
	36	X		X H36 to H48				X

Trial Day	Time (h)	PK Sampling (Plasma)	PK Sampling (Whole Blood)	PK Sampling (Urine)	Vital Signs	Meals	Postural Assessment of Heart Rate and Blood Pressure	12-lead ECG
				collection				
D10	48	X		X H48 to H72 collection	X	X		X
	55						X	
	56	X						X
D11	72	X			X			X
D15 (+/2 days)	168	X			X			X

[a] Allowable Time Windows for all procedures will be described in the Data Handling Protocol.
[b] Prior to dose