A Phase 1, Single Centre, Randomised, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of NeuroDirect Ketamine in Healthy Adult Volunteers

Protocol PSYCH007

Name and address of the sponsor and monitor (if other than the sponsor):	Psycheceutical, Inc. 515 E. Las Olas Blvd Suite 120 Fort Lauderdale, FL 33301 chad.harman@psycheceutical.com

PROTOCOL AUTHORISATION

Title: A Phase 1, Single-Centre Randomised, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of NeuroDirect Ketamine in Adult Healthy Volunteers

As Psycheceutical, Inc ("Sponsor") representative, I confirm that the study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the study drug, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

Signature	Date

INVESTIGATOR'S AGREEMENT

A Phase 1, Single-Centre Randomised, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of NeuroDirect Ketamine in Adult Healthy Volunteers

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), electronic Case Report Forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Human Research Ethics Committee (HREC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the Ethics Committee, except where necessary to avert an immediate hazard to the participants.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1): Guideline for GCP ICH E6 (R2), annotated with comments by the Australian Therapeutic Goods Administration (TGA; 2018).

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Investigational Site Nucleus Network

Dr. Ofer Gonen

Printed name of Principal Investigator

Signature of Principal Investigator

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sponsor Contact	Dr Sud Agarwal	+61 406 990 536 sud@ingenucro.com.au 15/456 St Kilda Rd Melbourne 3004
Sponsor Medical Monitor	Dr. Howard M. Wraight	+61 409 539 839 howard@hwraight.com.au c/o Ingenu @ 15/456 St Kilda Rd Melbourne 3004
Medical Monitor/24-hour Emergency Contact	Dr. Howard M. Wraight	+61 409 539 839 howard@hwraight.com.au c/o Ingenu @ 15/456 St Kilda Rd Melbourne 3004

Synopsis of Changes to the Protocol

Version #: 2

Previous Versions	Date
V 1	27December2022

Table 2. Summary of Changes from Version 1 to 2

Section	Change
Synopsis	Exclusion criteria amended to be consistent with Section 8.2.
7.1.2	Removed the need for review of PK data in sentinel patients. Consistent throughout protocol
7.5	Updated Schedule of Assessments as follows: • Screening (outpatient) timeframe from Day -28 to -2 • Admission to CRU on Day -1 and assessments moved from Day 1 to Day -1 • Added blood and urine sample collection for PK to Day 5 • Footnote 5 updated with correct FSH levels of ≥40 IU/L • Footnote 7 updated to reflect ECGs to be conducted at PK sampling timepoints
9.3.1	Randomization worded amended to state "randomized prior to dosing on Day 1" as randomization can often occur on Day 1 prior to dosing.
10.4	Removed the following statement: The dose will be measured using a syringe. Three mL of product will be drawn up and 1 mL will be extracted for administration.
10.5	Administration procedures updated to include: • Participant will be seated for 30 minutes post dose; changed from 5 minutes • Added statement: Participant should avoid touching the application site.
11	Updated study schedule to make consistent with updates made to Schedule of Assessments. Added BPRS assessments on the appropriate days
11.2.3	Day 5 added to post-dose assessments
12.1	Updated to clarify that there is no set time for the collection of urine and CSF, but should be as soon as possible after blood and urine/blood collection, respectively. Updated flushing with saline only (and not heparin) Amended PK blood collection timing from 0.05 hours to 0.5 hours Added Day 5 sampling times to Table 8.
13.1.7.4	COVID-19 testing separated from remaining serology as COVID-19 testing will occur on Day -1, while other serology will be completed at screening.

1. Synopsis

Name of Sponsor/Company:	Psycheceutical, Inc.
Name of Study Drug:	NeuroDirect Ketamine
Name of Active Ingredient:	Ketamine Hydrochloride
Protocol Number	PSYCH007
Title of Study:	A Phase 1, Single Centre, Randomised, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, of NeuroDirect Ketamine in Healthy Adult Volunteers
Phase of Development:	Phase 1
Study Centre(s)	Nucleus Network
Principal Investigator	Dr. Ofer Gonen
Study Period (Years):	Estimated date first participant enrolled: Estimated date last participant completed:
Objectives	**Primary:** To evaluate the safety and tolerability of NeuroDirect Ketamine following a single topical dose administration in healthy adult volunteers. **Secondary:** • To characterise the pharmacokinetic (PK) properties of NeuroDirect Ketamine and its major metabolite norketamine in plasma, CSF, and urine following a single topical dose administration. • To determine the maximum tolerated dose or the maximum feasible dose in the absence of establishing a maximum tolerated dose, and the recommended phase 2 dose of NeuroDirect Ketamine
Endpoints	**Primary:** Safety and tolerability will be assessed based on: • Frequency and severity of Treatment-Emergent Adverse Events and serous AEs (local and systemic) • Heart rate, blood pressures, 12- lead ECG • Clinical laboratory safety tests • Brief Psychiatric Rating Scale (BPRS) assessment to monitor hallucinations as a safety parameter **Secondary:** PK parameters will be calculated following single dosing and will include the following: o Maximum concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve (AUC) from time zero to the

	time of the last quantifiable concentration ($AUC_{0\text{-last}}$), AUC from time zero to time τ ($AUC_{0\text{-}\tau}$). ○ If the data are available, AUC from time zero to infinity ($AUC_{0\text{-inf}}$), terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F).
Methodology:	This is a phase 1, randomised, double-blind, placebo-controlled study to investigate the safety, tolerability, and pharmacokinetics of topically administered NeuroDirect Ketamine in a single-ascending dose study in adult healthy volunteers between 18-60 years of age, to establish the recommended phase 2 dose (RP2D). Oversight for the study will be provided by a Safety Review Committee (SRC) composed of the Principal Investigator (hereafter referred to as the Investigator), and the Sponsor's Medical Monitor (MM) and an Independent MM. The NeuroDirect Ketamine starting dose (i.e., for Cohort 1) will be 25 mg. The study plans to test single doses of NeuroDirect Ketamine of 25 mg (Cohort 1), 50 mg (Cohort 2), and 100 mg (Cohort 3). The decision to progress from Cohort 1 to Cohort 2 and Cohort 2 to Cohort 3 will be based on safety and tolerability by the SRC. A similar sequence will follow for subsequent progression decisions by the SRC for all the cohorts. Each part of the study will include a 28-day screening period, a treatment period, and follow-up period. Throughout this Study Protocol, timings for post-dose assessments ECG, blood, CSF, and urine samples for PK analysis are stated in relation to completion of the most recent dose of study drug. Serial blood samples, one CSF sample, and one urine sample for pharmacokinetic analysis will be collected at multiple time points through 72 hours post-dose for the single dose. A follow up visit will take place one-week post treatment. The participants will be enrolled into 1 of up to 3 sequential cohorts (Cohorts 1 to 3). Each cohort will consist of 8 participants (6 participants receiving NeuroDirect Ketamine and 2 participants receiving placebo). Potential study participants who provide voluntary written informed consent will undergo screening evaluations to determine eligibility within 28 days before the start of treatment (Day 1). Eligible participants will be admitted to the clinical research unit (CRU) on Day -1. Participants in each cohort will be administered a single topical dose of their allocated study drug (i.e., placebo or NeuroDirect Ketamine) on Day 1. In each cohort, 2 sentinel participants (1 randomised to NeuroDirect Ketamine and 1 randomised to placebo) will be dosed before proceeding with dosing of the remainder of the cohort. The Investigator will review safety and tolerability data (from at least the first 24 hours after dosing), before progression from sentinel participants to the remainder of the cohort. If desired, the Investigator may consult with the members of the SRC before deciding whether to proceed with the rest of the cohort. The Investigator must notify (in writing) the other members of the SRC of their decision to proceed or not with the rest of the cohort as soon as the decision is made. Participants will be required to remain in the CRU for 24 hours following dosing and then be discharged from the CRU. Participants will then follow up with daily outpatient visits until all post-dose assessments have been completed (i.e., Day 5). A final Follow-up visit will be scheduled for 7 (+ 3) days (i.e., Day 12 + 3 days). Study visits and assessments will occur as delineated in the Schedule of Assessments and PK samples will be collected prior to study drug administration and at different time intervals after dosing, as delineated in the PK Blood Sampling Schedule. Topical doses of NeuroDirect Ketamine at 25, 50, and 100 mg are planned. A decision to proceed from the current dose to the next higher dose will be made only

	after the SRC has reviewed all available safety, tolerability and PK (up to Day 5) data for the participants.
Number of Participants	Sufficient participants will be enrolled to obtain 24 evaluable subjects (8 per treatment arm; 6 treated and 2 placebo). Participants who withdraw or discontinue study medication may be replaced, unless the participant withdrew or stopped study medication due to treatment stopping criteria or a study drug -related adverse event (AE). The replacement participants will be assigned the same treatment sequence as the participants they are replacing.
Diagnosis:	The study will be conducted in healthy adult subjects
Main Criteria for Inclusion:	To be eligible for this study, participants must meet *all* of the following inclusion criteria: 1. Healthy male or female volunteers aged ≥ 18 to ≤ 60 years (inclusive) at the time of informed consent. 2. Capable of understanding the purposes and risks of the study and able to provide written informed consent before any study-specific screening procedures are performed. 3. Willing and able to adhere to all protocol requirements, including willingness to comply with scheduled visits. 4. Body weight ≥ 50 kg, and a body mass index (BMI; Quetelet index) in the range 18.0 to 32.0, inclusive. 5. Subject is free from clinically significant (in the opinion of the Investigator) illness or disease as determined by their medical and surgical history, physical examination, 12-lead ECG, vital signs and clinical laboratory determinations. 6. Adequate venous access in both arms for collection of a number of blood samples. 7. Negative urine drug/alcohol breath testing at Screening and prior to randomisation. Note: Screening urine drug test/alcohol breath testing may be repeated once if deemed appropriate by the Investigator. 8. Must have a negative COVID-19 PCR test on Day -1 9. If a subject is undergoing vaccination against Covid 19 virus, must wait 14 days after vaccination before first dose of investigational drug. 10. Female participants must meet 1 of the following criteria: a) Not of childbearing potential, defined as surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy - verbal confirmation through medical history review acceptable) or postmenopausal (i.e., no menses for at least 12 months). Postmenopausal status is to be confirmed by testing follicle-stimulating hormone [FSH] levels or local practice. b) Of childbearing potential and agrees to take effective contraceptive measures throughout the study period (i.e., highly effective birth control method such as hormonal contraception or intrauterine device [IUD], or abstinence, when in line with preferred or usual lifestyle), from study entry (i.e., Screening) until at least 3 months after the last dose of study drug. Contraception requirements do not apply for participants in an exclusively same-sex relationship. c) Of childbearing potential and in an exclusive relationship with a partner who has had a bilateral vasectomy at least 6 months prior to study entry. 11. Male participant: has undergone bilateral vasectomy (at least 6 months prior to study entry) and has documented evidence of azoospermia at least 90 days post procedure. or agrees to use effective contraceptive effective contraceptive measures (i.e. condoms for all types of sexual intercourse; plus use of a highly effective birth control method by their female partner, if they are of

	childbearing potential [see Inclusion Criteria 4]; or abstinence, when in line with preferred or usual lifestyle) and not donate sperm throughout the study period from study entry (i.e., Screening) until at least 3 months after the last dose of study drug.
Main Criteria for Exclusion:	A participant who meets any of the following exclusion criteria must be excluded from the study: 1. History of severe allergic or anaphylactic reactions, known intolerance, allergy or hypersensitivity reactions to Ketamine. 2. History of coronary disease, peripheral vascular disease, cerebrovascular accident, transient ischaemic attack, uncontrolled hypertension or signs/symptoms of ischaemic heart disease. 3. Mean baseline blood pressure above 130/80 mm Hg. 4. History of neurologic conditions such as seizures or convulsive disorders (including epilepsy), severe head injury or increased intracranial pressure. A history of childhood febrile seizures is allowed. 5. Presence of current psychiatric condition or psychiatric condition requiring pharmacological management within the last 6 months. 6. Positive results of a screen for PTSD through a validated PTSD rating scale questionnaire 7. A calculated creatinine clearance of < 85 mL/minute at Screening or pre randomisation according to the equation using Cockcroft and Gault. 8. Liver function tests showing values for ALT or AST > 1.5 times ULN at Screening. 9. Evidence or history of clinically significant (in the opinion of the Investigator) other cardiovascular, pulmonary, neurologic or renal disorders or hepatic, gastrointestinal, oral (difficulty swallowing / taking oral medication), haematological, endocrine, or psychiatric impairment/disorders. 10. Have undergone surgery requiring or have received (for any reason) anaesthetic within 30 days of Day 1, or planned surgery during the study. 11. Use of CNS depressants including opioids, sedative, anxiolytics, hypnotics, neuroleptics, phenothiazines, tranquilisers, skeletal muscle relaxants, sedating antihistamines or cimetidine within 30 days of Day 1. Use of macrolide antibiotics (e.g., Erythromycin), azole antifungal agents (e.g., Ketoconazole) or protease inhibitors (e.g., Ritonavir) within 30 days of Day 1. Thirty-day washout from these medications is required. 12. Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 1 month or 5 half-lives of the specific drug/biologic (whichever is longer) prior to dosing. 13. Donation or loss of more than 500 mL of blood within 30 days of Day 1 and/or plans to donate blood during the study. 14. Use of any prescription medication within 14 days of Day 1 and for duration of study, unless approved by both the Investigator and the Medical Monitor (in writing). If necessary, paracetamol (acetaminophen) or ondansetron (or other 5-HT3 receptor antagonist) may be administered with the approval of the Investigator. 15. Use of any over the counter product, herbal product, diet aid, or hormone supplement, with a particular regard to hemp or products containing cannabidiol, within 14 days of Day 1 and for duration of study, unless approved by both the Investigator and Medical Monitor (in writing). 16. Evidence or history of substance or alcohol abuse (drink more than 4 standard units of alcohol per day or >14 standard units per week), including positive results for the urine drugs of abuse test or a positive alcohol breath test at Screening or at Check-In (Day -1). 17. Unwilling or unable to abstain from recreational drug/substance use, from 48 hours before check-in until final study visit.

	18. Consumption of grapefruit, grapefruit juice or any products containing CYP3A4 inhibitors and inducers within 14 days of Day 1 and through to completion of the study. 19. Subjects who are not willing or are unable to refrain from nicotine products or smoking 24 hours before check-in until completion of the confinement period. 20. History of significant alcohol abuse within 6 months of screening or any indication of regular use of more than 14 units of alcohol per week for female subjects and 21 units of alcohol per week for male subjects (1 unit=360 mL of beer of 45 mL of alcohol 40%, or 150 mL of wine), and unwilling to refrain from consumption of alcohol from 24 hours before check-in until completion of the confinement period. 21. The use of more than 10 cigarettes, nicotine products per day or use of vaping device or e-cigarettes ten times per day within the past 30 days. 22. Unwilling or unable to abstain from caffeinated or other xanthine-containing products from check-in until completion of the confinement period. 23. Positive screening test for Human Immunodeficiency Virus (HIV) antibodies, Hepatitis B surface antigen or Hepatitis C antibody. 24. Malignancy within 5 years of screening visit (excluding non-melanoma skin cancer that has been resected). 25. Female subject that is pregnant or lactating. 26. Subject who is considered unsuitable for participating in the study in the opinion of the investigator.
Study Drug:	NeuroDirect Ketamine; topical ketamine
Dose and Mode of Administration:	Single dose of either 25 mg, 50 mg, or 100 mg applied via topical administration between C3 and C4 vertebrae
Duration of Treatment:	Following completion of an outpatient Screening Period (to be completed within a 26-day window), the expected duration of study participation and treatment is 12 days (including one day as an inpatient, 5 days of outpatient clinic visits, and one follow-up outpatient visit)
Reference Therapy and Mode of Administration:	Single dose of placebo control cream applied via topical administration between C3 and C4 vertebrae.
Criteria for Evaluation	**Safety and Tolerability:** Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, ECGs, and presence of hallucinations (using BPRS questionnaire). **Pharmacokinetics** PK parameters will be calculated from ketamine concentrations.
Statistical Methods:	Statistical methods will be further outlined in the statistical analysis plan (SAP) and approved by the Sponsor before any analysis. Procedures outlined in the SAP will supersede protocol-specified statistical methods in the event of divergence. All data in the database will be presented in by-participant data listings. Continuous variables will be summarised by dose and visit (where applicable), including the number of participants, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarised using the number of participants with frequency counts and percentages. For each treatment plasma, CSF, and urine concentrations or ketamine and norketamine will be tabulated and summarised by treatment and nominal time using descriptive statistics which include, but are not limited to: number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, minimum and maximum. If analytical data permit, the following PK parameters for ketamine and norketamine will be calculated:

	C_{max}, T_{max}, area under concentration-time curve (AUC), $AUC_{0\text{-}last}$, AUC0-τ, $AUC_{0\text{-}inf}$, $t_{1/2}$, CL/F. . **Analysis Populations:** Healthy volunteers' inclusion in each population will be determined before the final analysis. Safety Population: All participants who study drug will be included in the Safety Population. The Safety Population will be used for the summaries of all safety assessments. The Safety Population will be based on the actual dose level if the actual dose is different from the intended dose level. Pharmacokinetic Population: All participants who receive study drug and have a sufficiently evaluable concentration-time profile to allow determination of at least one PK parameter will be included in the PK population. An evaluable PK profile will be determined at the discretion of the pharmacokineticist following examination of participants with dosing or protocol deviations that could potentially affect the PK profile. The evaluable PK population will be used for the summaries of all PK data. **Safety Analyses:** All safety assessments, including AEs, laboratory evaluations, vital signs, ECGs, and other safety assessments, will be analysed using the Safety population. AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse event data will be listed for each participant, including verbatim term, preferred term (PT), system organ class (SOC), severity, and relationship to study drug will be provided. SOC and PT will summarise the number of participants experiencing TEAEs, and number of individual TEAEs. TEAEs will also be summarised by severity and by relationship to study drug. Laboratory evaluations (including haematology, coagulation, urinalysis, and serum chemistry) will be listed and summarised by treatment and protocol-specified collection time point. Observed and change from baseline (Day 1 prior to dosing) clinical laboratory data will be summarised each protocol-specified collection time point. Vital signs (systolic and diastolic blood pressure, pulse rate, aural [tympanic] temperature, respiratory rate, and clinical laboratory tests), summary statistics for ECG parameters will be listed and summarised by treatment and protocol-specified collection time point. Observed and actual value will be summarised at each protocol-specified collection time point. ECG values will be listed and summarised by treatment and dose level. A summary of change from baseline (Day 1 prior to dosing) at each protocol-specified time point will also be presented. The Investigator's clinical assessment of whether the ECG result was considered 'normal', 'abnormal but not clinically significant'; or 'abnormal and clinically significant' will also be reported.