Statistical Analysis Plan

A Double-Blind, Placebo-controlled, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) and CSF Capture Study of the Safety, Pharmacokinetics and Pharmacodynamics of (2R,6R)-Hydroxynorketamine in Healthy Volunteers

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Prepared by:	Pharmacometrics and Small Trials Program Duke Clinical Research Institute Durham, North Carolina

SAP SIGNATURE PAGE AND APPROVALS

Shruti Raja, MD Principal Investigator Duke Clinical Research Center Duke Department of Neurology	Signature and Date
Carlos Zarate, MD Sponsor Signatory National Institute of Mental Health Hatfield Clinical Research Center	Signature and Date
Jesse DeLaRosa, MStat Biostatistician Duke Clinical Research Institute Interventional Statistics group	Signature and Date
Christoph Hornik, MD, PhD, MPH Director, Pharmacometrics Center Duke Clinical Research Institute Duke Department of Pediatrics	Signature and Date

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	Aspartate aminotransferase
BMI	Body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CADSS	Clinician Administered Dissociative States Scale
CMO	Contract manufacturing organization
CRF	Case report form
CSF	Cerebrospinal Fluid
DCRI	Duke Clinical Research Institute
DEPRU	Duke Early Phase Research Unit
ECG	Electrocardiogram
FDA	Food and Drug Administration
FFT	Fast Fourier Transform
FSH	Follicle-stimulating hormone
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HED	Human equivalent dose
HEK	Human embryonic kidney
hERG	Human ether-á-go-go-related gene
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IDP	Investigational drug product
IP	Intraperitoneal
IRB	Institutional Review Board
IV	Intravenous
Ln	Log transformation
MAD	Multiple ascending dose
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MOP	Manual of Procedures
NMDAR	NMDA-type glutamate receptors
NOAEL	No observed adverse effect levels
PD	Pharmacodynamic
PHI	Protected health information
PI	Principal Investigator
PK	Pharmacokinetic(s)
POMS	Profile of Mood States
PQC	Product quality complaint

qEEG	Quantitative electroencephalography
SAD	Single ascending dose
SAE	Serious adverse event
SAR	Suspected adverse reaction
SOC	Summarized by system organ class
SQ	Subcutaneous
TRD	Treatment-resistant depression
WHO	World Health Organization

1. Study Title

A Double-Blind, Placebo-controlled, Single Ascending Dose (SAD), Multiple Ascending Dose (MAD) and CSF Capture Study of the Safety, Pharmacokinetics and Pharmacodynamics of (2R,6R)-Hydroxynorketamine in Healthy Volunteers

2. Study Synopsis

Title:	A Double-Blind, Placebo-controlled, Single Ascending Dose (SAD), Multiple Ascending Dose (MAD) and CSF Capture Study of the Safety, Pharmacokinetics and Pharmacodynamics of (2R,6R)-Hydroxynorketamine in Healthy Volunteers
Sponsor	National Institute of Mental Health
Name of Drug Substance	(2R,6R)-Hydroxynorketamine hydrochloride
Name of investigational drug product	(2R,6R)-Hydroxynorketamine hydrochloride solution for injection
Clinical Phase	Phase I
Clinical Site	Duke Clinical Research Institute, Duke University School of Medicine
Objectives	Primary: • Determine the safe dose range of (2R,6R)-Hydroxynorketamine • Determine the pharmacokinetics of (2R,6R)-Hydroxynorketamine administered in single ascending doses • Determine the pharmacokinetics of (2R,6R)-Hydroxynorketamine administered in multiple ascending doses Secondary: • Collect quantitative electroencephalography (qEEG) data following administration of (2R,6R)-Hydroxynorketamine in healthy Subjects as a pharmacodynamic biomarker • Determine the pharmacokinetics of (2R,6R)-Hydroxynorketamine in cerebral spinal fluid (CSF) following a single IV administration

Methodology/Study Design	A 6-cohort single ascending dose (SAD) study will be conducted in healthy volunteers utilizing a slow-infusion intravenous (IV) route of administration. Standard safety, pharmacokinetics (PK) and qEEG monitoring will be evaluated at all dose levels. Subsequently, a 2-cohort multiple ascending dose (MAD) study will be conducted. Doses will be administered on days 1,4, 8, and 11. Standard safety parameters will be monitored, and PK will be evaluated at all dose levels. Finally, one cohort of healthy volunteers will receive a single dose by slow-infusion IV and have PK samples collected from both blood and cerebrospinal fluid (CSF).
Safety	Safety will be assessed throughout the study. Baseline and follow-up safety assessments will include height, body mass index (BMI), weight, temperature, medical, visual and ocular history, physical examinations, ocular examinations, visual acuity, color vision tests, electrocardiograms (ECGs), vital signs (VS), clinical laboratory tests (hematology, serum chemistry, and urinalysis), the Profile of Mood States (POMS), the Columbia-Suicide Severity Rating Scale (C-SSRS), the Clinician Administered Dissociative States Scale (CADSS), and adverse events (AEs). Safety assessments will include AEs, ECGs, VS, clinical laboratory results, and physical observations. Assessment of each Subject's level of alertness/sedation will be accomplished using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S). Evaluation of safety in the MAD study will utilize the same safety assessments used in the SAD study. Monitoring of AEs will be governed by change from baselines established during prescreening and Day -1 examinations and clinical laboratory tests. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term, by severity, by relationship to study drug and study procedure, and by study drug dose. Dose escalation in the SAD study or continued dosing in the MAD study may be stopped according to the predefined halting rules or if a Subject's scores demonstrate acute suicidality on the C-SSRS assessment or at the discretion of the study Principal Investigator and/or sponsor. Determination of whether to escalate to the next dose level in the SAD study or continue dosing in the MAD will be made by the Principal Investigator in consultation with the Medical Monitor and Study Sponsor.

Test products, dose, and mode of administration for SAD study	Cohort 1: (2R,6R)-Hydroxynorketamine @ 0.1 mg/kg via slow IV infusion (40 minutes) Cohort 2: (2R,6R)-Hydroxynorketamine @ 0.25 mg/kg via slow IV infusion (40 minutes) Cohort 3: (2R,6R)-Hydroxynorketamine @ 0.5 mg/kg via slow IV infusion (40 minutes) Cohort 4: (2R,6R)-Hydroxynorketamine @ 1.0 mg/kg via slow IV infusion (40 minutes) Cohort 5: (2R,6R)-Hydroxynorketamine @ 2.0 mg/kg via slow IV infusion (40 minutes) Cohort 6: (2R,6R)-Hydroxynorketamine @ 4.0 mg/kg via slow IV infusion (40 minutes)
Test products, mode of administration and schedule for MAD study	Cohort 1: (2R,6R)-Hydroxynorketamine @ 1.0 mg/kg via slow IV infusion (40 minutes) on days 1, 4, 8, 11 Cohort 2: (2R,6R)-Hydroxynorketamine @ 2.0 mg/kg via slow IV infusion (40 minutes) on days 1, 4, 8, 11 Control product (placebo) will be sterile saline also administered via slow IV infusion (40 minutes). The highest dose administered in the MAD will not exceed the highest tolerable SAD dose.
Test products, mode of administration and schedule for CSF capture study	Cohort 1: (2R,6R)-Hydroxynorketamine @ 0.25 mg/kg via slow IV infusion (40 minutes) Control product (placebo) will be sterile saline also administered via slow IV infusion (40 minutes).
Duration of patient participation in study	Participants in the SAD study: each Subject will participate in one treatment period. A treatment period consists of residential stay on days -1 to 2 inclusive with 1 follow up visit (Day 3) and phone call (Day 5-8). Participants in the MAD study: each Subject will participate in one treatment period. A treatment period consists of residential stay on days -1 to 11 inclusive with 1 follow up visit (Day 12) and phone call (Day 17-19). Participants in the CSF capture study: each Subject will participate in one treatment period. A treatment period consists of residential stay on days -1 to 2 inclusive with 1 follow up visit (Day 3) and phone call (Day 5-8).

Study populations	All the SAD, MAD, and CSF populations will be made up of healthy male and female adult volunteers (aged 18-65 years) who meet all defined inclusion/exclusion criteria.

3. Schedule of Assessments and Procedures

3.1 SAD Schedule of Assessments and Procedures

	Screening	Study Period				
Procedure	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5-8**
Informed Consent	X					
Eligibility Criteria	X	X				
Demographics	X					
Height	X					
Weight, BMI	X	X			X	
Medical history	X	X			X	X
Physical Examination*	X	X		X	X	
Vital Signs**	X	X	X	X	X	
ECG**	X	X	X	X	X	
Urine Drug Test	X	X				
Urine Cotinine	X	X				
Alcohol Breath Test	X	X				
Pregnancy Test (Females)^	X	X				
Serology (Hepatitis B, Hepatitis C, HIV)	X					
Clinical Lab. Tests (Hema., Chem., Urinalysis)	X	X	X	X		
Prior and Concom. Meds.	X	X		X	X	X
Ocular Examinations***		X			X	
Modified Observer's Assess. of Alert./Sed. (MOAA/S)****			X			
Suicide Screen (C-SSRS)	X	X	X	X		
Mood and Cognitive Assessment (POMS)		X	X	X		X
Clin. Admin. Diss. States Scale (CADSS)*****		X	X			
IV Drug Administration			X			
Blood Sample Collection (PK)			X	X	X	
Urine Sample Collection (PK)			X	X		
qEEG			X			
Confinement		X	X	X		
Adverse Events			X	X	X	X
Outpatient Visit					X	
Phone Call						X

An early termination visit will be scheduled on an ad hoc basis for any subject who withdraws from the study.
* Physical examinations can be conducted at any additional time at the judgement of the Principal Investigator (eg,
to evaluate an adverse event)
^FSH for postmenopausal women at screening visit
** Day 1 Timepoints: 1-hr preinfusion, and 1, 2, 4, 8, and 12 hr after the start of the infusion.
*** Ocular examinations include visual acuity and color vision tests.
**** On Day 1, MOAA/S is performed preinfusion, during the infusion at approximately 20 min after start of
infusion, 40 min after start of infusion, and approximately 1 hr after the start of the infusion.
***** On Day 1, CADSS is performed preinfusion and approximately 40 min and 80 min after the start of the
infusion.

3.2 MAD Schedule of Assessments and Procedures

Procedure	**Screening (Day –28 to Day -2)**	**Confinement**										**Follow-Up**	
		Day -1	**Day 1**	**Day 2**	**Day 4**	**Day 5**	**Day 7**	**Day 8**	**Day 9**	**Day 11**	**Day 12**	**Day 15**	**Day 17-19**
Informed Consent	**X**												
Eligibility Criteria	**X**	**X**											
Demographics	**X**												
Height	**X**												
Weight, BMI	**X**	**X**									**X**		
Medical history	**X**	**X**									**X**	**X**	**X**
Physical Examination*	**X**	**X**					**X**				**X**		
Vital Signs**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**		
ECG**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Urine Drug Test	**X**	**X**					**X**						
Alcohol Breath Test	**X**	**X**					**X**						
Pregnancy Test (Females)^	**X**	**X**					**X**						
Serology (Hepatitis C, Hepatitis B, HIV)	**X**												
Clinical Lab. Tests (Hema., Chem., Urinalysis)	**X**		**X**	**X**				**X**	**X**	**X**	**X**		
Prior and Concom. Meds.	**X**	**X**	**X**			**X**	**X**				**X**	**X**	**X**
Ocular Examinations***		**X**		**X**						**X**	**X**		
Modified Observer's Assess. of Alert./Sed. (MOAA/S)****			**X**		**X**			**X**		**X**			
Suicide Screening (C-SSRS)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Mood and Cognitive Assessment (POMS)		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Clin. Admin. Diss. States Scale (CADSS)*****			**X**		**X**			**X**		**X**			
IV Drug Administration			**X**		**X**			**X**		**X**			
Blood Sample Coll. (PK)			**X**	**X**	**X**			**X**		**X**	**X**		

Check-in & Confinement		**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**			
Check-out******						**X**					**X**		
Adverse Events			**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Outpatient Visit													
Phone Call												**X**	**X**

An early termination visit will be scheduled on an ad hoc basis for any subject who withdraws from the study.
* Physical examinations can be conducted at any additional time at the judgement of the Principal Investigator (eg, to evaluate an adverse event)
^FSH for postmenopausal women at screening
** Dosing Day timepoints: 1-hr preinfusion, and 1, 2, 4, 8, and 12 hr after the start of the infusion.
*** Ocular examinations include visual acuity and color vision tests.
**** On Dosing days MOAA/S is performed preinfusion, during the infusion at approximately 20min after start of infusion, 40 min after start of infusion, and approximately 1 hr after the start of the infusion.
***** On Dosing days, CADSS is performed preinfusion and approximately 40 min and 80 min after the start of the infusion.

3.3 CSF Capture Study Schedule of Assessments and Procedures

Procedure	**Screening (Day –28 to Day -2)**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5-8**
Informed Consent	**X**					
Eligibility Criteria	**X**	**X**				
Demographics	**X**					
Height	**X**					
Weight, BMI	**X**	**X**			**X**	
Medical history	**X**	**X**			**X**	**X**
Physical Examination*	**X**	**X**		**X**	**X**	
Vital Signs**	**X**	**X**	**X**	**X**	**X**	
ECG**	**X**	**X**	**X**	**X**	**X**	
Urine Drug Test	**X**	**X**				
Urine Cotinine	**X**	**X**				
Alcohol Breath Test	**X**	**X**				
Pregnancy Test (Females)^	**X**	**X**				
Serology (Hepatitis B, Hepatitis C, HIV)	**X**					
Clinical Lab. Tests (Hema., Chem., Urinalysis)	**X**	**X**	**X**	**X**		
Prior and Concom. Meds.	**X**	**X**		**X**	**X**	**X**
Ocular Examinations***		**X**			**X**	
Suicide Screen (C-SSRS)	**X**	**X**	**X**	**X**		
Mood and Cognitive Assessment (POMS)		**X**	**X**	**X**		**X**
IV Drug Administration			**X**			
Blood Sample Collection (PK)			**X**	**X**		
Cerebrospinal Fluid Collection (PK)			**X**			
Confinement		**----------X----------**				

Adverse Events			**X**	**X**	**X**	**X**
Outpatient Visit					**X**	
Phone Call						**X**

An early termination visit will be scheduled on an ad hoc basis for any subject who withdraws from the study.
* Physical examinations can be conducted at any additional time at the judgement of the Principal Investigator (eg, to evaluate an adverse event)
^FSH for postmenopausal women at screening visit
** Day 1 Timepoints: 1-hr preinfusion, and 1, 2, 4, 8, and 12 hr after the start of the infusion.
*** Ocular examinations include visual acuity and color vision tests.

4. Study Objectives and Endpoints

4.1 Primary:

The primary objective of this study is to determine the safe dose range and tolerability of (2R,6R)-Hydroxynorketamine HCl administered via a slow IV infusion (40 minutes) to healthy volunteers. A second primary objective for this study is to assess the pharmacokinetics (PK) of (2R,6R)-Hydroxynorketamine HCl.

4.2 Secondary:

The secondary objective of this study is to collect quantitative electroencephalography (qEEG) data as a PD biomarker. Analysis of qEEG is not included as part of the proposed Statistical Analysis Plan (SAP).

4.3 Study Endpoints:

Study endpoints include completion of all dosing levels and timepoints with full collection of all safety data, adverse events (AEs) tabulation, clinical laboratory tests, PK endpoints (eg, Cmax, time to Cmax [tmax], minimum plasma concentration [Cmin], area under the plasma concentration-time curve from 0 to infinity [AUC0-], area under the plasma concentration-time curve during the dosing interval [AUC0-Tau], systemic plasma clearance (CL), volume of distribution during terminal phase [Vz], renal clearance [CLR], terminal half-life [t1/2]), and qEEG measurements..

5. Study Design

5.1 Study Design (SAD)

This is a 6-cohort, single site, first-in human, double-blind, placebo-controlled, randomized single ascending dose (SAD) study assessing (2R,6R)-Hydroxynorketamine in healthy male and female volunteers. All Subjects in the SAD study will undergo a screening period of up to 28 days to ensure that all eligibility requirements are met. Key baseline safety metrics will be taken during screening and on the first Day of

confinement. Selected safety metrics will be collected during the on-drug portion of the study. A final safety assessment will be conducted via an outpatient visit and follow-up phone call.

All cohorts will include 6 Subjects receiving drug and 2 Subjects receiving placebo. All cohorts will incorporate sentinel dosing of 1 active and 1 placebo Subject. Each Subject will only participate in a single dose level. Table 1 outlines the planned dosing levels and number of Subjects in each cohort.

Each treatment will be administered after Subjects have fasted overnight for at least 8 hours.

Table 1: SAD planned dosing levels

Cohort	Dose (mg/kg)	Subjects on Active Drug (n)	Subjects on Placebo (n)
1A (Sentinel 1)	0.1	1	1
1B	0.1	5	1
2A (Sentinel 2)	0.25	1	1
2B	0.25	5	1
3A (Sentinel 3)	0.5	1	1
3B	0.5	5	1
4A (Sentinel 4)	1.0	1	1
4B	1.0	5	1
5A (Sentinel 5)	2.0	1	1
5B	2.0	5	1
6A (Sentinel 6)	4.0	1	1
6B	4.0	5	1

5.2 Study Design (MAD)

The multiple ascending dose (MAD) portion of the study is a 2-cohort single site, double-blind, placebo-controlled design assessing (2R,6R)-Hydroxynorketamine in healthy male and female volunteers. All Subjects in the MAD study will undergo a screening period of up to 28 days to ensure that all eligibility requirements are met. Key baseline safety metrics will be taken during screening and on the first Day of confinement. Selected safety metrics will be collected during the on-drug portion of the study. A final safety assessment will be conducted via an outpatient visit and follow-up phone call.

All cohorts will include 6 Subjects receiving drug and 2 Subjects receiving placebo. Each Subject will receive a total of 4 doses (drug or placebo) administered on days 1, 4, 8, and 11. Each Subject will only participate in a single dose level. Table 2 outlines the planned dosing levels and number of Subjects in each cohort.

Each dose will be administered after Subjects have fasted overnight for at least 8 hours.

Table 2: MAD planned dosing levels

Cohort	Dose (mg/kg)	Subjects on Active Drug (n)	Subjects on Placebo (n)
1	1.0	6	2
2	2.0	6	2

5.3 Study Design (CSF)

The single dose capture study (CSF) portion of the study is a 2-cohort single site, double-blind, placebo-controlled design assessing (2R,6R)-Hydroxynorketamine in healthy male and female volunteers. All Subjects in the CSF study will undergo a screening period of up to 28 days to ensure that all eligibility requirements are met. Key baseline safety metrics will be taken during screening and on the first Day of confinement. Selected safety metrics will be collected during the on-drug portion of the study. A final safety assessment will be conducted via an outpatient visit and follow-up phone call.

All cohorts will include 5 Subjects receiving drug and 3 Subjects receiving placebo. Each Subject will only participate in a single dose level. Table 3 outlines the planned dosing levels and number of Subjects in each cohort.

Each dose will be administered after Subjects have fasted overnight for at least 8 hours.

Table 3: CSF planned dosing levels

Cohort	Dose (mg/kg)	Subjects on Active Drug (n)	Subjects on Placebo (n)
1	0.25	5	3

5.4 Selection of Study Population

Healthy male and female adult subjects (18-65 years old) will be enrolled in this study. It is expected that the PK of (2R,6R)-Hydroxynorketamine in these Subjects will be representative of the PK profile in patients with TRD. The cohort size in all SAD and MAD stages is expected to sufficiently evaluate the safety and PK of (2R,6R)-Hydroxynorketamine. Furthermore, these cohort sizes are also expected to provide sufficient qEEG data to evaluate the use of qEEG as a potential PD biomarker. Analysis of qEEG is not included as part of the proposed Statistical Analysis Plan (SAP).

5.5 Treatment Assignment

5.5.1 Randomization Procedures

All Subjects and clinical staff, (except the unblinded pharmacy staff) will be blinded to treatment. An unblinded pharmacist staff will be required at the Clinical Site to comply with the study's randomization and blinding requirements. At the clinical site, prior to study administration, the PI will be responsible for designating a qualified pharmacy staff

to serve as the unblinded pharmacy staff in the study. Unblinded pharmacy staff may dose Subjects, but may not participate in Subject assessments.

The designated, unblinded pharmacy staff will be responsible for all drug accountability issues, including preparing, labelling, and dispensing study drug and placebo in accordance with the randomization codes provided, yet remain independent of all Subject assessments. The pharmacy staff will follow the Standard Operating Procedures and Work instructions related to pharmacy services and protocol-specific requirements.

Randomization codes will be provided to the unblinded pharmacy staff. Confirmation of receipt of the randomization code will be required by the Sponsor. The unblinded pharmacy staff will be responsible for maintaining the blind, consistent with protocol design, throughout the study. All documentation is to be filed in the Pharmacy Manual. Access to this manual will be restricted to the unblinded pharmacy staff.

The Subjects, PI, and all other study personnel involved with the Subject assessments will be blinded to the actual treatment assignment of the Subjects. The PI will be ultimately responsible for ensuring the integrity of the blind, and that it is maintained through the study.

The treatment assignment should only be unblinded at the clinic in the case of dose limiting toxicity or emergency when the knowledge of the study drug assignment is necessary for the clinical management or welfare of the Subject. Breaking the blind at the clinic under any other circumstance will be considered a protocol violation. The PI is strongly encouraged to contact the sponsor before unblinding the study drug assignment. If the blind is broken for any reason, the Investigator must notify the Sponsor within one day. In addition, the Investigator will record the date and reason for revealing the blinded study drug assignment for that Subject in the source documents and appropriate case report form page(s).

6. Populations for Analysis

6.1 Randomized Population

All participants who are randomized to treatment assignment.

6.2 Safety Population

All participants who received at least one dose of study medication. This includes any subjects who were replaced and received at least one dose.

6.3 PK Population

All participants who have at least one interpretable PK sample. PK population will be further defined in the PK Analysis Plan

6.4 qEEG Population

qEEG population will be defined in the qEEG Analysis Plan.

6.5 On Treatment Population

All participants who completed all doses for their treatment group.

7. General Analysis Conventions

Analyses will be stratified by treatment assignment, dose groups, and sub studies (SAD, MAD, CSF):

- SAD
  - Cohorts 1 through 6 (2R,6R)-Hydroxynorketamine individually
  - Overall (2R,6R)-Hydroxynorketamine
  - Overall placebo
- MAD
  - Cohorts 1 through 2 (2R,6R)-Hydroxynorketamine individually
  - Overall (2R,6R)-Hydroxynorketamine
  - Overall placebo
- CSF
  - Cohort 1 (2R,6R)-Hydroxynorketamine individually
  - Overall placebo

General statistical approaches are presented below.

All subjects in the Safety Population will be included in the safety analysis grouped by study, cohort, and treatment group. Statistical analysis of safety data will be descriptive.

Baseline is defined as the last non-missing assessment prior to dosing of study medication.

For continuous variables, summaries will include sample size, mean, median, 25^{th} and 75^{th} percentiles, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. No inferential hypothesis testing will be performed. Repeat or unscheduled results will not be included in the summaries, but will be listed. Data from placebo subjects will be pooled for final presentations.

Missing data results will not be imputed. Data summaries and analyses (e.g. means) will be calculated using all available data. If the start day for an AE is missing, day of study drug administration will be used and AE will be considered treatment emergent. Neither month nor year will be imputed for AE.

Planned analyses are descriptive or exploratory. If presented, significance level and confidence intervals will use alpha of 0.05. No adjustments for multiple testing are planned.

Analyses will be performed using a UNIX server based installation of SAS Software, version 9.4 or newer.

8. Outcomes

8.1 Primary Outcome Measures

Study outcomes include

- Completion of all dosing levels and timepoints with full collection of all safety data
- Adverse event (AE) tabulation
- Clinical laboratory tests

8.2 Secondary Outcome Measures

8.2.1 Pharmacokinetics

Analysis of this outcome will be covered by the separate PK Analysis Plan.

8.2.2 qEEG

Analysis of this outcome will be covered by the separate qEEG Analysis Plan.

9. Analysis Endpoints

9.1 Primary Endpoints

The primary endpoints are the following:

1) Study Drug Exposure
2) Concomitant Medications
3) Safety Analysis
4) Adverse Events
5) Clinical Laboratory Results
6) Vital Signs
7) Physical Examinations
8) Ocular Examinations
9) Mood and Cognitive Assessment (POMS)
10) Suicide Screen (C-SSRS)
11) Clinician Administered Dissociative States Scale
12) Modified Observer's Assessment of Alertness/Sedation Scale (MOASS)

9.2 Pharmacodynamics Endpoints

A second primary objective for this study is to assess the pharmacokinetics (PK) of (2R,6R)-Hydroxynorketamine HCl. PK endpoint analyses are covered in the PK analysis plan.

9.3 qEEG Endpoints

The secondary objective of this study is to collect quantitative electroencephalography (qEEG) data as a PD biomarker. qEEG endpoint analyses are covered in the qEEG analysis plan.

10. Sample Size

A total of 48 Subjects are planned to be enrolled in a 6-cohort SAD study (36 in the treatment groups and 12 in the control groups).

All SAD cohorts will have 6 Subjects in the treatment group and 2 Subjects in placebo group. All cohorts in the SAD study will incorporate sentinel dosing which will include 1 active and 1 placebo Subject. All remaining Subjects will be dosed at least 24 hours after the sentinel cohort participants.

A total of 16 Subjects are planned to be enrolled in a 2 cohort MAD study (12 in the treatment groups and 4 in the control groups). All MAD cohorts will have 6 Subjects in the treatment group and 2 Subjects in placebo group.

A total of 8 subjects are planned to be enrolled in a 1 cohort CSF capture study. The CSF cohort will have 5 in the treatment group and 3 in the control group.

Additional cohorts (both SAD and MAD) may be enrolled if it is determined that an intermediate or higher dose level should be evaluated upon review of both safety and PK data. The Institutional Review Board will be notified of this revised approach.

11. Analyses and Reporting

11.1 Final Analyses

All final, planned analyses identified in this SAP will be performed only after the last participant has completed the last study visit, safety period and had end of study assessments, and all relevant study data have been processed and integrated into the analysis database. In addition, no database may be locked or analyses completed until this SAP has been approved. Unblinding of treatment assignments will not occur until the data are locked.

12. Planned Analyses

The Safety Population will be used for all analyses unless otherwise specified.

12.1 Subject Disposition

Analysis populations will be summarized by study (SAD/MAD/CSF), cohort, and treatment assignment. The Safety Population will be used for any additional Subject Disposition analyses.

The number and percentage of subjects who completed and prematurely discontinued the study will be presented by study drug and overall vs placebo for the Randomized Population. Reasons for premature discontinuation as recorded on the completion page of the CRF will be summarized, as applicable.

12.2 Demographics and Baseline Characteristics

The Safety Population will be used for Demographic and Baseline Characteristics analyses.

Demographic and baseline characteristics (e.g. age, weight) will be summarized and listed by study cohort and treatment assignment.

Medical history will be summarized by system organ class and preferred term. Terms will be coded using MedDRA 23.1 or higher. Terms will also be listed, including verbatim term and condition onset date.

12.3 Study Drug Exposure

The Safety Population will be used for all Study Drug Exposure analyses.

Study drug exposure will be summarized by study (SAD/MAD/CSF), treatment assignment, and dose group. Individual patient listings will also be provided.

12.4 Concomitant Medications

Concomitant medications will be listed, along with available information on dose, route, frequency, and used to treat AE. Terms will be coded using B3 WHO Drug General.

12.5 Safety Analyses

The Safety Population will be used for all safety analyses unless otherwise indicated. All analyses will include summaries by treatment group and study cohort. All summaries will be supported by data listings.

12.6 Adverse Events

An adverse event (AE) is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a clinical trial. (Any change in clinical status, routine labs, x-rays, physical examinations, etc.), that is considered clinically significant by the study investigator is considered an AE. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary.

Adverse reaction is any adverse event caused by the drug. Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. A reasonable possibility implies that there is evidence that the drug caused

the event. An event will be considered Related to study drug if the investigator deems the event relationship as Possible, Probably, or Definite. An event is Not Related if the investigator classified the event relationship to study drug as Unlikely or Not Related. Expectedness and Severity (Mild, Moderate, Severe) of event will also be collected.

An AE or Suspected Adverse Reaction (SAR) or Adverse Reaction is considered "Serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event (SAE) when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.7 Clinical Laboratory Results

Summary statistics of observed and change from baseline data will be presented for each treatment group, cohort, and dose where applicable. Shift tables summarizing the numbers of subjects shifting from normal pre-dose values to abnormal post-dose values will also be presented where applicable.

Lab tests included will be all in the hematology and coagulation panel, biochemistry panel, and urinalysis panel (as needed lab tests: RBC, WBC, hyaline casts, cellular casts, and granular casts will only be presented as listings).

Listings for all safety laboratory evaluations will also be presented.

12.8 Vital Signs

Vital signs (supine systolic and diastolic blood pressure, heart rate/pulse, body temperature) and changes from baseline at each time point will be presented by treatment group and cohort.

Listings for all vital signs will be presented.

12.9 Physical Examinations

Descriptive statistics for weight and BMI at baseline and changes from baseline at each assessment time point will be presented by treatment group and cohort.

A listing of physical examination data for all subjects will be provided.

12.10 Ocular Examinations

Descriptive statistics for visual acuity and color vision at baseline and changes from baseline at each assessment time point will be presented by treatment group and cohort.

A listing of ocular examination data for all subjects will be provided.

12.11 Mood and Cognitive Assessment (POMS)

Descriptive statistics for total mood disturbance (TMD) at baseline and changes from baseline at each assessment time point will be presented by treatment group and cohort.

A listing of POMS data for all subjects will be provided.

12.12 Suicide Screen (C-SSRS)

Descriptive statistics for suicidal behavior or ideations will not be provided.

12.13 Clinician Administered Dissociative States Scale (CADSS)

Descriptive statistics for CADSS total score at baseline and changes from baseline at each assessment time point will be presented by treatment group and cohort.

A listing of CADSS data for all subjects will be provided.

12.14 Modified Observer's Assessment of Alertness/Sediation Scale (MOAAS)

Descriptive statistics for MOAAS total score not equal to 5 will be presented by treatment group and cohort.

A listing of MOASS data for all subjects as described above will be provided.

13. Appendix

13.1 References

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subcutaneous tralokinumab in Japanese healthy volunteers. *Drug Metab Pharmacokinet*. 2018;33(3):150-158.
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13.2 Appendix 1: MOAA's:

Responsiveness scores of the Modified Observer's Assessment of Alertness/sedation Scale.

Response	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly of repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

13.3 Appendix 2: POMS:

Abbreviated POMS (Revised Version)

Name:_____ Date:

Below is a list of words that describe feelings people have. Please **CIRCLE THE NUMBER THAT BEST DESCRIBES HOW YOU FEEL <u>RIGHT NOW</u>**.

	Not At All	A Little	Moderately	Quite a lot	Extremely
Tense	0	1	2	3	4
Angry	0	1	2	3	4
Worn Out	0	1	2	3	4
Unhappy	0	1	2	3	4
Proud	0	1	2	3	4
Lively	0	1	2	3	4
Confused	0	1	2	3	4
Sad	0	1	2	3	4
Active	0	1	2	3	4
On-edge	0	1	2	3	4
Grouchy	0	1	2	3	4
Ashamed	0	1	2	3	4
Energetic	0	1	2	3	4
Hopeless	0	1	2	3	4
Uneasy	0	1	2	3	4
Restless	0	1	2	3	4
Unable to concentrate	0	1	2	3	4
Fatigued	0	1	2	3	4
Competent	0	1	2	3	4
Annoyed	0	1	2	3	4
Discouraged	0	1	2	3	4
Resentful	0	1	2	3	4
Nervous	0	1	2	3	4

Miserable	0	1	2	3	4

PLEASE CONTINUE WITH THE ITEMS ON THE NEXT PAGE

	Not At All	A Little	Moderately	Quite a lot	Extremely
Confident	0	1	2	3	4
Bitter	0	1	2	3	4
Exhausted	0	1	2	3	4
Anxious	0	1	2	3	4
Helpless	0	1	2	3	4
Weary	0	1	2	3	4
Satisfied	0	1	2	3	4
Bewildered	0	1	2	3	4
Furious	0	1	2	3	4
Full of Pep	0	1	2	3	4
Worthless	0	1	2	3	4
Forgetful	0	1	2	3	4
Vigorous	0	1	2	3	4
Uncertain about things	0	1	2	3	4
Bushed	0	1	2	3	4
Embarrassed	0	1	2	3	4

Citation:
Grove, J.R., & Prapavessis, H. (1992).
Preliminary evidence for the reliability and validity
of an abbreviated Profile of Mood States.
International Journal of Sport Psychology, 23,
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***** SCORING KEY *****

Scores for the seven subscales in the abbreviated POMS are calculated by summing the numerical ratings for items that contribute to each subscale. The correspondence between items and subscales is shown below.

Item	**Scale**	Not At All	A Little	Moderate	Quite a lot	Extremely
Tense	**TEN**	0	1	2	3	4
Angry	**ANG**	0	1	2	3	4
Worn Out	**FAT**	0	1	2	3	4
Unhappy	**DEP**	0	1	2	3	4
Proud	**ERA**	0	1	2	3	4
Lively	**VIG**	0	1	2	3	4
Confused	**CON**	0	1	2	3	4
Sad	**DEP**	0	1	2	3	4
Active	**VIG**	0	1	2	3	4
On-edge	**TEN**	0	1	2	3	4
Grouchy	**ANG**	0	1	2	3	4
Ashamed	**ERA**	Reverse-score this item [0 = 4, 1 = 3, 2 = 2, 3 = 1, 4 = 0]				
Energetic	**VIG**	0	1	2	3	4
Hopeless	**DEP**	0	1	2	3	4
Uneasy	**TEN**	0	1	2	3	4
Restless	**TEN**	0	1	2	3	4
Can’t concentrate	**CON**	0	1	2	3	4
Fatigued	**FAT**	0	1	2	3	4
Competent	**ERA**	0	1	2	3	4
Annoyed	**ANG**	0	1	2	3	4
Discouraged	**DEP**	0	1	2	3	4
Resentful	**ANG**	0	1	2	3	4
Nervous	**TEN**	0	1	2	3	4
Miserable	**DEP**	0	1	2	3	4

Item	Scale	Not At All	A Little	Moderate	Quite a lot	Extremely
Confident	**ERA**	0	1	2	3	4
Bitter	**ANG**	0	1	2	3	4
Exhausted	**FAT**	0	1	2	3	4
Anxious	**TEN**	0	1	2	3	4
Helpless	**DEP**	0	1	2	3	4
Weary	**FAT**	0	1	2	3	4
Satisfied	**ERA**	0	1	2	3	4
Bewildered	**CON**	0	1	2	3	4
Furious	**ANG**	0	1	2	3	4
Full of Pep	**VIG**	0	1	2	3	4
Worthless	**DEP**	0	1	2	3	4
Forgetful	**CON**	0	1	2	3	4
Vigorous	**VIG**	0	1	2	3	4
Uncertain…	**CON**	0	1	2	3	4
Bushed	**FAT**	0	1	2	3	4
Embarrassed	**ERA**	Reverse-score this item [0 = 4, 1 = 3, 2 = 2, 3 = 1, 4 = 0]				

TEN = Tension	Note that 2 of the items on the Esteem-related Affect (ERA) subscale are reverse-scored prior to being combined with the other items.
ANG = Anger	

FAT = Fatigue	**Total Mood Disturbance (TMD)** is calculated by summing the totals for the negative subscales and then subtracting the totals for the positive subscales: TMD = [TEN+DEP+ANG+FAT+CON] – [VIG+ERA]. A constant (e.g., 100) can be added to the TMD formula in order to eliminate negative scores.
DEP = Depression	
ERA = Esteem-related Affect	
VIG = Vigour	
CON = Confusion	

13.4 Appendix 3: C-CSSR:

COLUMBIA-SUICIDE SEVERITY RATING SCALE
(C-SSRS)
Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 - 130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation*** <u>Past X Months</u> - ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe

Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others on and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted	**Yes** ☐ **No** ☐ Total # of interrupted
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted	**Yes** ☐ **No** ☐ Total # of aborted

Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:			**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?			**Yes** ☐	**No** ☐	**Yes** ☐	**No** ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:			
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code*	*Enter Code*	*Enter Code*			
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code*	*Enter Code*	*Enter Code*			

13.5 Appendix 4: CADSS:

The Clinician Administered Dissociative States Scale (CADSS)

Name_____ ID_____ Date_____

Subjective Items:

1. Do things seem to be moving in slow motion?
0= Not at all.
1= Mild, things seem slightly slowed down, but not very noticeable.
2= Moderate, things are moving about twice as slow as normally.
3= Severe, things are moving so slowly that they are barely moving.
4= Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.

2. Do things seem to be unreal to you, as if you are in a dream?
0= Not at all.
1= Mild, things seem a little unreal, but I'm well aware of where I'm at.
2= Moderate, things seem dreamlike, although I know I am awake.
3= Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.
4= Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.

3. Do you have some experience that separates you from what is happening;
for instance, do you feel as if you are in a movie or a play, or as if you are a robot?
0= Not at all.
1= Mild, I feel a little bit separated from what is happening, but I am basically here.
2= Moderate, I feel somewhat separated from what is going on, or I feel as if I am in a movie or a play.
3= Severe, I feel extremely separated from what is happening, but I can understand what people are saying.
4= Extreme, I feel as if everyone around me is talking a foreign language, so that I cannot understand what they are saying, or I feel as if I am on the outside looking in, or like I am a robot or a machine.

4. Do you feel as if you are looking at things from outside of your body?
0= Not at all.
1= Mild, I feel somewhat disconnected from myself, but I am basically all together.
2= Moderate, I feel like I am just outside of my body, but not looking down upon myself from far above.
3= Severe, I feel like I am twenty feet or more away from my body, looking down from above.
4= Extreme, I feel as if I am hundreds of feet above myself, looking down at myself and everyone else here.

5. Do you feel as if you are watching the situation as an observer or a spectator?
0= Not at all.

1= Mild, I feel slightly detached from what is going on, but I am basically here.
2= Moderate, I feel somewhat removed as an observer or a spectator, but I am definitely in this room.
3= Severe, I feel very much as if I am an observer or a spectator, but I am still here in this room.
4= Extreme, I feel completely removed from what is happening, as if I am not a part of this experience in any way, but totally removed from what is happening, as an observer or a spectator.

6. Do you feel disconnected from your own body?
0= Not at all.
1= Mild, I feel a little bit disconnected from myself, but I am basically all here.
2= Moderate, I feel somewhat detached from my own body, but I am basically all together.
3= Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.
4= Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.

7. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?
0= Not at all.
1= Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.
2= Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.
3= Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.
4= Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.

8. Do people seem motionless, dead, or mechanical?
0= Not at all.
1= Mild, people seem a little bit more motionless, dead, or mechanical than would be normal.
2= Moderate, people seem to be at least twice as motionless or mechanical than would be normal.
3= Severe, people seem to be barely moving, or barely alive, or very mechanical.
4= Extreme, it's as if everyone were frozen or completely like machines.

9. Do objects look different than you would expect?
0= Not at all.
1= Mild, things seem slightly different than normal, although it is barely perceptible.
2= Moderate, things are somewhat distorted, but I have no problems recognizing things around me.
3= Severe, things are much more distorted or unreal than normal, but I am able to recognize things in the room.
4= Extreme, like everything is distorted, not real, I feel like I cannot recognize anything, everything is alien or strange.

10. Do colors seem to be diminished in intensity?
0= Not at all.
1= Mild, things seem slightly paler than usual if I think about it.
2= Moderate, colors are somewhat diminished, but still recognizable.
3= Severe, colors are extremely pale, in no way as vivid as they usually are.
4= Extreme, as if everything is in black and white, or all the colors have been washed out.

11. Do you see things as if you were in a tunnel, or looking through a wide angle photographic lens?
0= Not at all.
1= Mild, I feel a little bit like I am looking through a tunnel, or a wide angle lens.
2= Moderate, the periphery of my vision is blacked out, but I still have most of my visual field, or things are somewhat like a wide angle lens.
3= Severe, it seems as if I'm looking through a tunnel, or through a wide angle lens, but I can see everything clearly.
4= Extreme, as if I'm looking through a pair of binoculars backwards, where everything around the periphery is blacked out, and I can see a little point of light at the end of a tunnel, with little tiny people and objects, or I am seeing things as if through a wide lens and things are incredibly expanded.

12. Does this interview [assessment, questionnaire] seem to be taking much longer than you would have expected?
0= Not at all.
1= Mild, it seems as if this interview has gone on for at least twice as long as the true elapsed time.
2= Moderate, it seems as if this interview has gone on for at least two hours.
3= Severe, it seems as if at least ten hours have gone on since the start of the interview.
4= Extreme, it seems as if time is standing still, so that we have been here at this point in time forever.

13. Do things seem to be happening very quickly, as if there is a lifetime in a moment?
0= Not at all.
1= Mild, things are happening slightly faster than normal.
2= Moderate, things seem to be happening at least twice as fast as normal.
3= Severe, things seem to be happening at least 10 times faster than normal.
4= Extreme, as if this whole experience has happened at once, or as if there is a lifetime in a moment.

14. Have there been things which have happened during this interview [assessment] that now you can't account for?
0= Not at all.
1= Mild, there may have been things which happened which now I can't account for, but nothing pronounced.
2= Moderate, at least once there were things which happened which now I can't account for.
3= Severe, at least twice I have lost several minutes of time, so that now there are things I cannot account for.
4= Extreme, large pieces of time are missing, of ten minutes or more, so that I am

confused about what has happened.

15. Have you spaced out, or in some other way lost track of what was going on during this experience?
0= Not at all.
1= Mild, I have had some episodes of losing track of what is going on, but I have followed everything for the most part.
2= Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.
3= Severe, I have lost several segments of time of one minute or more.
4= Extreme, I have lost large segments of time of at least 15 minutes or more.

16. Have sounds almost disappeared or become much stronger than you would have expected?
0= Not at all.
1= Mild, things are either a little quieter than normal, or a little louder than normal, but it is not very noticeable.
2= Moderate, things have become about twice as soft as normal, or twice as loud as normal.
3= Severe, things have become very quiet, as if everyone is whispering, or things have become very loud (although not deafening).
4= Extreme, things have become completely silent, or sounds are so loud that it is deafening, and I feel as if I am going to break my eardrums.

17. Do things seem very real, as if there is a special sense of clarity?
0= Not at all.
1= Mild, things seem to be a little bit more real than normal.
2= Moderate, things seem to be more real than normal.
3= Severe, things seem to be very real or have a special sense of clarity.
4= Extreme, things seem to have an incredible sense of realness or clarity.

18. Does it seem as if you are looking at the world through a fog, so that people and objects appear far away or unclear?
0= Not at all.
1= Mild, things seem somewhat foggy and unclear, or I do have the feeling that things are far away, but there is not a major effect on how I perceive things around me.
2= Moderate, things seem very foggy and unclear, or things seem like they are far away, but I can identify the interviewer and objects in the room easily.
3= Severe, I can barely see things around me, such as the interviewer and the objects in the room.
4= Extreme, I cannot make anything out around me.

19. Do colors seem much brighter than you would have expected?
0= Not at all.
1= Mild, colors seem a little bit brighter than normal, but not more than twice as bright.
2= Moderate, colors seem brighter, about twice as bright as normal.
3= Severe, colors seem very bright, at least five times as bright as normal.
4= Extreme, colors seem extremely bright, almost fluorescent, at least 10 times as

bright as normal.

20. Do you feel confused about who you really are?
0= Not at all.
1= Mild, I feel a little bit confused about who I am.
2= Moderate, I feel confused about who I am, but I basically know who I am.
3= Severe, I feel very confused about who I am, and at times I wonder if I am a person, or if I am many people.
4= Extreme, I feel as if there were two or more sides to myself.

21. Do you feel like there are different parts of yourself which do not fit together?
0= Not at all.
1= Mild, I feel like there are different sides of myself, but they're basically part of myself.
2= Moderate, I feel like I have different parts which don't quite fit together.
3= Severe, there are two or more sides to myself which have unique characteristics.
4= Extreme, I have two or more parts to myself with unique personality characteristics.

22. Do you have gaps in your memory?
0= Not at all.
1= Mild, there are some recent things which I cannot remember.
2= Moderate, there have been a few gaps in my memory which lasted a few minutes.
3= Severe, there have been large gaps in my memory which lasted for more than a few minutes.
4= Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

23. Do you feel like you have more than one identity?
0= Not at all.
1= Mild, I feel like there is more to me than my personality, but it's basically part of my identity.
2= Moderate, I feel like I have more than one personality, but the personalities are not really distinct.
3= Severe, I have two or more personalities, although they are not fully developed as distinct entities.
4= Extreme, I have two or more personalities which are distinct and have their own names and other unique characteristic