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Brief Title: Cognitive Behavioral Therapy Following Esketamine for Major Depression and Suicidal Ideation for Relapse Prevention

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CBT-ENDURE: Cognitive Behavioral Therapy following Esketamine for Major Depression and Suicidal Ideation for Relapse Prevention

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List of Abbreviations

AE	Adverse Event
BDI	Beck Depression Inventory
BSI	Beck Scale for Suicidal Ideation
CBT	Cognitive Behavioral Therapy
CCBT	Computer-assisted CBT
CGI-SI	Clinician Global Impression Scale for Suicidal Ideation
CRF	Case Report Form
CSSRS	Columbia Suicide Severity Rating Scale
CTAS	Cognitive Therapy Awareness Scale
DSMB	Data and Safety Monitoring Board
EC	Executive Committee
ECT	Electroconvulsive Therapy
eCRF	Electronic Case Report Form
ED	Emergency Department
EOT	End-of-Treatment
Esk	Esketamine
FDA	Food and Drug Administration
GDA	Good Days Ahead
ICF	Informed Consent Form
IRB	Institutional Review Board
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MDSI	Major Depression with Suicidal Ideation
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MINI	Mini International Neuropsychiatric Interview
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PROs	Patient Reported Outcomes
REMS	Risk Evaluation and Mitigation Strategy
RFA	Request for Applications
RRS	Ruminative Response Scale
SAE	Serious Adverse Event
SAFTEE	Systematic Assessment for Treatment Emergent Effects
SI	Suicidal Ideation
SOC	Standard of Care
SoCT	Skills of Cognitive Therapy
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
TAU	Treatment as Usual
TRD	Treatment-resistant Depression
WIRB	Western Institutional Review Board
YCAS	Yale Center for Analytical Sciences
3PRLT	3-Option Probabilistic Reversal Learning Task

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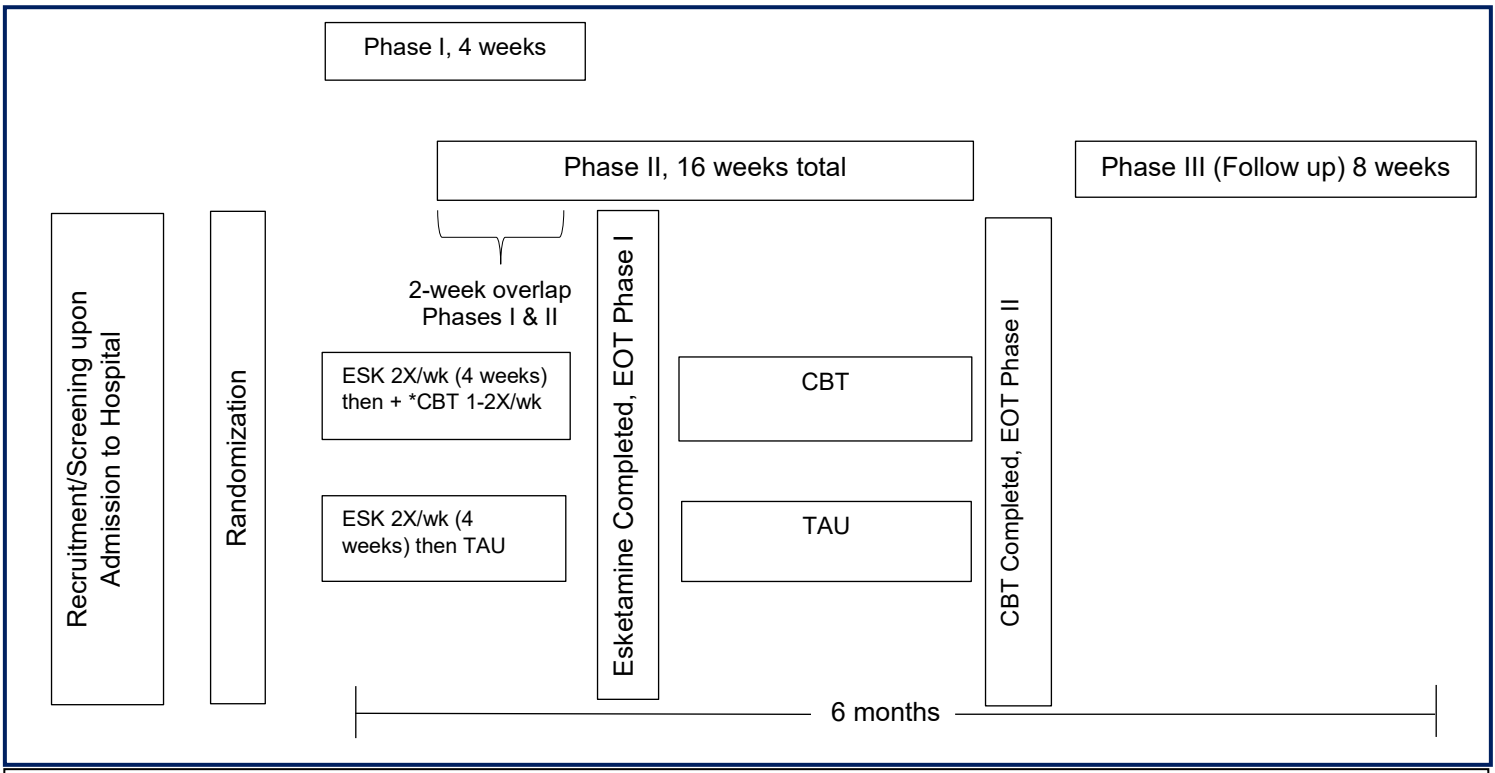
1. STUDY SYNOPSIS

Title	CBT-ENDURE: Cognitive Behavioral Therapy following Esketamine for Major Depression and Suicidal Ideation for Relapse Prevention
Funding Agency	National Institute of Mental Health
Study Centers	Yale University (coordinating center) University of Alabama-Birmingham (delayed start) University of Pennsylvania (delayed start)
Patient Population	Individuals with major depression who are admitted to a psychiatric hospital due to suicidal ideation or attempt
Study Objectives	**Specific Aim 1**: To determine the feasibility and safety of performing a larger study examining the effectiveness and mechanism of action of CBT to improve the longer-term outcomes following esketamine treatment in patients hospitalized for suicidal ideation or suicide attempt. **Specific Aim 2**: To evaluate the appropriateness and utility of the proposed tests of cognitive control measures in exploring the mechanisms underlying the effects on depression of esketamine and the combination of esketamine+CBT. **Specific Aim 3**: To examine the efficacy of esketamine+CBT combination compared to esketamine+TAU in reducing suicidal ideation.
Study Design	This is a rater-blinded, randomized controlled trial. All patients will receive esketamine for treatment of Major Depression with Suicidal Ideation (MDSI). Subjects will be randomized (1:1) to receive CBT (computer-assisted) or TAU alone following esketamine.
Number of Participants	Approximately 60 eligible participants will be enrolled and randomized, 30 in the CBT arm and 30 in the TAU-only arm.
Duration of Study	We expect to start recruitment at Yale in January 2021, with additional sites coming on board within 12 months of this date. Recruitment will wrap up around Feb/Mar of 2024.
Duration of Patient Participation	Barring attrition, each participant will be followed for 6 months.
Key Eligibility Criteria	Inclusion: 1) Written informed consent before any study procedures are performed 2) Meeting criteria for inpatient admission for suicidal ideation or attempt at one of the study sites 3) Recommended by a physician for esketamine treatment 4) Males or females ages 18 through 65 years of age 5) Diagnosis of major depressive disorder as confirmed by the MINI 6) Willing to adhere to a reliable form of contraception throughout the trial and for one month following completion of the trial (for subjects who are sexually active) 7) In the opinion of the investigator, the patient is willing and able to comply with scheduled visits, treatment plan, and other trial procedures for the duration of the study Exclusion: 1) Active substance use disorder (except tobacco) within 6 months of screening date

	2) Meets DSM-5 criteria for bipolar disorder, schizophrenia, schizophreniform disorder, schizoaffective disorder, or pervasive development disorder 3) Dementia or other cognitive disorder or intellectual disability that would impair the subject's ability to meaningfully engage in CBT (per investigator judgment) 4) Any other medical or psychiatric comorbidity that the investigator judges would put the participant at additional undue risk due to study participation or would impair subject's ability to participate in the study. 5) Current or planned participation in a formal CBT program defined by the following characteristics, each session has an agenda, a homework assignment is given at each session, and the homework assignment from the previous session is reviewed at the following appointment. 6) Previous Esketamine or ketamine treatment that did not produce a clinical response as outlined below. • 6 treatments with Esketamine at a dose of 56 mg or more with no clinical response • 6 treatments of IV ketamine at a dose between 0.4 mg/kg and 0.7mg /kg with no clinical response Patients must not have received Esketamine or ketamine treatment within the past 12 weeks of time of enrollment. 7) The patient is pregnant or breastfeeding 8) Unable to give informed consent 9) Was previously enrolled/randomized into the trial 10) Patients who have a contraindication to receiving Esketamine including any of the following: • aneurysmal vascular disease • arteriovenous malformation • history of intracerebral hemorrhage • hypersensitivity to esketamine or ketamine
Interventions	Esketamine: All participants will receive esketamine for MDSI (Major depression with suicidal ideation) as part of their standard care. The protocol will adhere to the FDA label for this product and the FDA-registered trials. The starting dose will be 84mg instranasal, with subsequent dose adjustments for tolerability. Subjects will receive 8 total esketamine treatments, given twice per week for 4 weeks. Pre-procedural medical workup, monitoring and observation requirements will follow the Esketamine REMS and each site's clinical protocol. CBT: Half of participants will be randomized to the CBT intervention, which will consist of an in-person and computer-based component (based on Good Days Ahead). In total, this will consist of 20 total sessions given over 16 weeks (the first 4 weeks of CBT will have sessions twice weekly; thereafter sessions will be held weekly). TAU only:

	Participants not randomized to CBT will undergo treatment as usual (TAU). These patients will undergo standard, post-hospitalization clinical treatments, which may include physician visits and psychotherapy (except for formal CBT).
Concomitant Medications	All patients will continue their existing antidepressant treatment while on the study protocol. Patients will also continue existing non-psychotropic medications initiated prior to the Baseline/Visit 1, unless the investigator determines that they are contraindicated for esketamine treatment. Each site will follow their standard clinical protocol for this. Given the patient population, medications may be adjusted by study or community physicians in the best interest of the safety of the patient.
Prohibited Therapies	Patients will not be permitted to undergo electroconvulsive therapy (ECT) concurrently with esketamine therapy or formal CBT (outside the study) at any point while enrolled in the study.
Outcome Measures and Analysis	The primary outcomes for this study will be rates of recruitment, attrition, and serious adverse events. We will also conduct group comparisons on suicidal ideation over 6 months using a general, linear-mixed model. The outcome measures for suicidal ideation will be: 1) The Beck Scale for Suicidal Ideation 2) The Columbia Suicide Severity Rating Scale 3) Item 10 of the Montgomery-Asberg Depression Rating Scale 4) The Clinician Global Impression for Suicide Severity We will also conduct preliminary analyses of neurocognitive measures and the strength of correlation between clinical status and cognitive functioning. The primary scales to use in this will be the Emotional Stroop and Emotional N-Back.

1.1 Trial Schema



Trial Schema. Study Overview. ESK – esketamine; CBT – cognitive behavioral therapy; TAU – treatment as usual; EOT – end of treatment. *For those randomized to CBT group, they will begin CBT after 2 weeks of open-label esketamine.

2. BACKGROUND AND RATIONALE

Suicide is among the top 10 causes of mortality worldwide,[1,2] with over 47,000 suicides in the United States in 2017.[3] Unfortunately, despite renewed public efforts to confront this problem, suicide rates have increased by 24%[4] and suicide-related ED visits have increased 42%[3] in the last 20 years. Approximately 90% of individuals who commit suicide suffer from a treatable psychiatric disorder,[5,6] most commonly major depressive disorder (MDD). Recently, the director of the National Institute of Mental Health has called for a renewed effort to combat this public health problem and reduce the rate of suicide.

The period following psychiatric hospitalization is one of extreme high risk for suicide.

A converging line of research has identified that the time period following a psychiatric hospitalization as one of great risk for suicide.[7,8] A recent meta-analysis of 100 studies with 183 samples reported patients discharged from psychiatric hospitalization are at high risk for suicide; the post-discharge suicide rate was approximately 150 times the suicide rate of the general population (2,078 per 100,000 person-years v. 14 per 100,000 person-years); notably, these post-hospitalization suicide rates are higher now compared to previous decades.[9] Hence, providing therapies and services that reduce risk of suicide in the period following psychiatric hospitalization may provide an opportunity to meaningfully impact the rate of suicide

and suicide attempts. Ketamine and esketamine may provide ways to treat patients during this period of high risk, but relapse rates following discontinuation of treatment are high.

Current therapies for patients at risk of suicide are limited.
Few therapies have been shown to reduce the risk of suicide. Clozapine is FDA-approved for "reducing the risk of recurrent suicidal behavior", but this comes from studies in patients with schizophrenia, not mood disorders, which constitute the largest portion of patients who commit suicide.[10] Significant evidence supports a reduction in the long-term risk of suicide in mood disorders associated with lithium treatment.[11] However, the anti-suicidal benefits of lithium are not evident in the short-term and providers are hesitant to prescribe it to patients at acute risk of suicide given the risks associated with lithium overdose. Standard oral antidepressant treatments (e.g., SSRIs) reduce suicidal ideation,[12] but their effects are delayed and a subset of younger patients can experience transient worsening of ideation or self-injury.[13-15] *These limitations highlight the need for more effective and rapidly acting treatments that reduce suicidal ideation and suicide risk.*

Ketamine has emerged as an antidepressant with rapid effects on suicidal ideation.
Over the last decade, a series of studies has demonstrated the ability of ketamine to act as a robust and rapid-acting antidepressant.[16,17] In early 2019, the US Food and Drug Administration (FDA) approved esketamine nasal spray as an augmentation strategy for treatment-resistant depression (TRD). In August 2020, the FDA approved a supplemental indication for esketamine for use in major depression with suicidal ideation (MDSI).

Questions and concerns remain about the long-term treatment plan with esketamine/ketamine. Despite the promise and excitement of using ketamine/esketamine to rapidly stabilize depressed patients in need of hospitalization due to suicide risk, the long-term therapeutic plan is unclear. The Phase 3 studies of esketamine in MDSI recruited patients from emergency department settings who needed hospitalization. However, the protocol used treatment paradigm only provides treatment for 4 weeks. Given the extremely high risk of suicide in the 6-12 months following psychiatric hospitalization, this treatment paradigm leaves many unanswered questions regarding the longer-term management of these severely ill patients. Furthermore, even if esketamine is provided over a longer-term period, there is serious concern about the potential long-term adverse effects that may result from indefinite and repeated treatments. Hence, there is a great need for maintenance strategies capable of sustaining ketamine's effects that may minimize ketamine exposure, especially in this high-risk population of patients hospitalized for suicidal ideation or attempts.

Cognitive behavioral therapy (CBT) may sustain ketamine's therapeutic effects.

Cognitive behavioral therapy (CBT) effectively augments classic antidepressant medications and is highly effective in relapse prevention, especially among those with previous recurrent episodes.[18,19] CBT has also been shown to prevent suicide attempts in high risk populations over longer-term periods.[20,21] In one randomized trial of patients who had recently attempted suicide (N=120), CBT reduced the risk of subsequent suicide attempts over the following 18 months by 42% (24.1% versus 41.6%).[20] In a more recent study of a military sample (N=152), CBT was also shown to reduce the rate of suicide attempts compared to TAU over a period of 2 years by 66% (13.8% versus 44.2%).[21] Work by our group demonstrates the feasibility and potential benefit of combining ketamine and CBT to sustain the anti-depressant effects of ketamine in severely ill, TRD patients. A promising, open-label pilot study (N=8) showed a relapse rate of 25% at 8 weeks following last ketamine infusion[22], which compares favorably to historical data, where relapse rates are 55-70% at 4 weeks.[23,24] A preliminary analysis of an ongoing early investigator study (PI Wilkinson) finds early evidence of CBT relapse prevention effects for 28 ketamine treated MDD patients in a randomized study (**Figure 1**), consistent with the open-label study. Here we see preliminary evidence suggesting a sustaining antidepressant effect of CBT compared to treatment as usual (TAU) patients over a period of 14 weeks following last ketamine. These results are consistent with prior literature showing that CBT is effective in patients not previously responsive to medication[25] and that it can reduce relapse after prior effective medication treatment.[26]

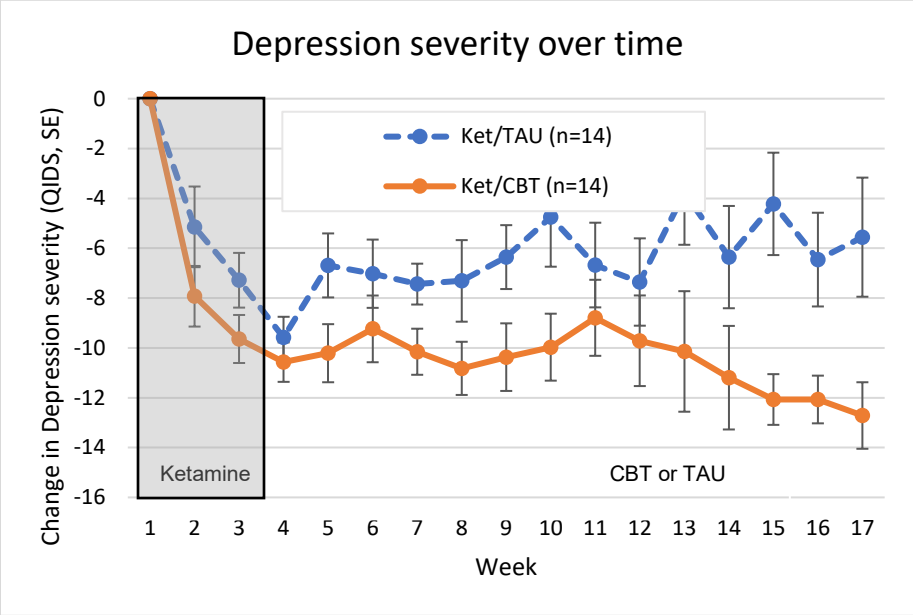


Figure 1. Depression severity for up to 14 weeks following ketamine in a proof-of-concept randomized trial (unpublished data). TAU – treatment as usual; CBT – cognitive behavioral therapy; QIDS – Quick inventory of depressive symptomatology;

While our group has accrued significant experience using ketamine and CBT in patients with TRD and suicidal ideation, the primary objective of the current proposal is to conduct a *feasibility and safety study of esketamine followed by CBT in patients at risk of suicide who need hospitalization. Data from this project will assist in planning for a large, well-powered study that evaluates effectiveness as well as a possible mechanism by which CBT might sustain esketamine's effects during an extremely high-risk period.*

CBT is not readily available in the community; computer-assisted CBT may improve access. About 1.3 million people are admitted to hospitals in the US annually for suicidal ideation or attempt. Unfortunately, substantial problems exist with the dissemination of CBT. Foremost among these problems is a lack of well-trained CBT therapists. While a high proportion (69% in one study[27]) of community therapists report using CBT techniques, a very

small portion actually have formal training in this method or apply CBT in a rigorous manner.[28] Given the high number of patients and the low availability of CBT, computer-assisted CBT (CCBT) has been developed to improve access to CBT while maintaining high fidelity to traditional, in-person CBT models. The version of CCBT to be used in this protocol— Good Days Ahead—is designed not to replace therapists entirely but 1) to reduce the total time required for therapists to successfully administer CBT to each patient; 2) to reduce specialized training time required to administer CBT effectively; and 3) to improve fidelity of CBT implemented in community settings. Good Days Ahead (GDA) has been shown to be non-inferior to traditional, in-person CBT and has been used in several federally funded projects (R18-HS-024047; R01-MH-082762; R01-MH-082794).[29,30]

Significance of the proposed study. The proposed study is of central relevance to the NIMH Strategic Plan of striving for prevention and cures (Objective 3) and strengthening the public health impact of NIMH-supported research (Objective 4). In particular, this study focuses on the NIMH priority of addressing rising rates of suicide, which has been a priority of the NIMH and its director, Dr. Gordon. Results from this feasibility and safety study will allow for a larger, well-powered clinical trial that potentially use outcomes of suicidal behaviors (a critical gap in ketamine literature). Furthermore, given the rapid increase in ketamine use by community providers (including long-term use), which currently outpaces research, as well as the concerns of adverse clinical sequelae resulting from long-term ketamine exposure (abuse liability, bladder and neurotoxicity), the proposed study is both timely and of critical importance to the field.

3. STUDY DESIGN

This study is a prospective, randomized controlled, 2-arm (1:1 ratio), clinical trial of esketamine+CBT+TAU v. esketamine+TAU for the treatment of major depression with suicidal ideation (MDSI). The current project is composed of three phases: Phase I – Esketamine Treatment Phase; Phase II – CBT Treatment Phase (for those randomized to CBT); and Phase III – Follow-up Phase. Phases I and II overlap for a period of 2 weeks. Following recruitment and enrollment, eligible patients with MDD who are presenting to emergency department settings or inpatient units and consent to participation will undergo 4 weeks of standard care intranasal esketamine treatment. Phase II will begin after two weeks of esketamine (4 treatments), at which point participants assigned to CBT arm begin computer-assisted CBT. Participants cannot receive electroconvulsive therapy concurrently with esketamine treatment. If a participant begins ECT after esketamine treatment they will continue on protocol. Patients in the TAU group can receive other therapies as indicated by the treating physician with the exception of CBT. Phase III will be comprised of additional follow-up, during which patients will be contacted for assessments every 4 weeks.

All subjects will complete self-reported and clinician-administered questionnaires throughout the study (see Schedule of Events).

3.1 OUTCOME MEASURES

This is a feasibility study to assess whether we can successfully recruit severely ill patients in a manner that is safe and feasible for a larger, well-powered trial. We will

therefore measure rates of recruitment per site per month. We will also measure retention.

Patient-Reported Outcomes (PROs)
PROs include the Beck Depression Inventory, the Beck Scale for Suicidal Ideation.,. These will be completed throughout the trial.

Clinician-Reported Measures
These include the Montgomery-Asberg Depression Rating Scale (MADRS), the Columbia Suicide Severity Rating Scale (CSSRS) and the Clinician Global Impression Scale for Suicidal Ideation (CGI-SI). These will be conducted every 2 weeks throughout the trial. The MADRS and CSSRS will be conducted by a blinded rater.

For Esketamine, CBT, and TAU visits, preference will be that all scales are administered within a 24-hour period before treatment visits. However, a 24-hour post-visit window will be permitted, so long as participants are not assessed within 6 hours of esketamine.

4. SUBJECT SELECTION AND PARTICIPANTS

4.1 Recruitment of Trial Participants

Patients with MDSI who are in need of hospitalization and who are also candidates for esketamine will be screened as potential participants for the study. Potential participants will be approached after the decision to admit and treat with esketamine has been made. At this time, the patient will be informed about the study and given a thorough explanation of risks, benefits, study procedures and expectations. Those who consent to study participations will sign written informed consent. They will then undergo a screening visit immediately (it is expected that this will likely occur on the same day as signed informed consent but will be permissible for up to 5 days following consent).

4.2 Inclusion Criteria

Participants are eligible for the study if they meet all the following criteria:

1) Written informed consent before any study procedures are performed
2) Meeting criteria for inpatient admission for suicidal ideation or attempt at one of the study sites
3) Recommended by a physician for esketamine treatment
4) Males or females ages 18 through 65 years of age
5) Diagnosis of major depressive disorder as confirmed by the MINI
6) Willing to adhere to a reliable form of contraception throughout the trial and for one month following completion of the trial (for subjects who are sexually active)

7) In the opinion of the investigator, the patient is willing and able to comply with scheduled visits, treatment plan, and other trial procedures for the duration of the study

4.3 Exclusion Criteria

Participants are excluded if they meet any of the following criteria:

1) Active substance use disorder (except tobacco) within 6 months of screening date
2) Meets DSM-5 criteria for bipolar disorder, schizophrenia, schizophreniform disorder, schizoaffective disorder, or pervasive development disorder
3) Dementia or other cognitive disorder or intellectual disability that would impair the subject's ability to meaningfully engage in CBT (per investigator judgment)
4) Any other medical or psychiatric comorbidity that the investigator judges would put the participant at additional undue risk due to study participation or would impair subject's ability to participate in the study.
5) Current or planned participation in a formal CBT program defined by the following characteristics, each session has an agenda, a homework assignment is given at each session, and the homework assignment from the previous session is reviewed at the following appointment.
6) Previous Esketamine or ketamine treatment that did not produce a clinical response as outlined below.
    - 6 treatments with Esketamine at a dose of 56 mg or more with no clinical response
    - 6 treatments of IV ketamine at a dose between 0.4 mg/kg and 0.7mg /kg with no clinical response

    Patients must not have received Esketamine or ketamine treatment within the past 12 weeks of time of enrollment.
7) The patient is pregnant or breastfeeding
8) Unable to give informed consent
9) Was previously enrolled/randomized into the trial
10) Patients who have a contraindication to receiving Esketamine including any of the following:
    - aneurysmal vascular disease
    - arteriovenous malformation
    - history of intracerebral hemorrhage
    - hypersensitivity to esketamine or ketamine

5. STUDY TREATMENTS

5.1 Phase I: Acute Esketamine Treatment Phase

Following screening procedures, participants will be treated in an open-label fashion with a 4-week, 8-treatment course of esketamine nasal spray. This protocol is based on

the clinical trials that led to the FDA label for this indication.[31-33] Pre-procedure medical evaluation (physical examination, electrocardiogram, etc.) will be in accordance with the US FDA label for esketamine and in accordance with each site's clinic policy. Notably, the pre-procedural medical workup is part of the clinical care procedures and not part of study data collected.

Dosing will begin with the 84mg dose, according to the FDA approved label. The dose can be lowered for tolerability reasons for any treatment following the first. Dose information will be recorded on the CRF.

Participants will receive esketamine treatment twice weekly for 4 weeks, per the FDA label. Some flexibility will be permitted (in case of scheduling difficulties or medical reasons) to allow participants two extra weeks to complete the Esketamine Treatment Phase (Phase I).

During Phase I, participants will complete Patient Reported Outcomes (PROs) clinician-administered assessments at Baseline/Visit 1, Visit 3a, and Phase I End-of-treatment (EOT) Visit (Week 5). In addition, the Ruminative Response Scale (RRS), Skills of Cognitive Therapy (SoCT) and Cognitive Therapy Awareness Scale (CTAS) will be done at Baseline/Visit 1, Visit 3a. The RRS SoCT and CTAS are patient-reported outcomes that assess the intensity of ruminations of subjects (RRS) and how subjects respond to stressful situations (SoCT and CTAS).

5.2 Phase 2: Cognitive behavioral therapy (CBT) or treatment as usual (TAU)

Phase 2 will overlap with Phase 1 by two weeks and will begin after a subject has completed 4 esketamine treatments. Starting at Phase 2, study protocol will differ depending on which treatment group the participant has been randomized into.

Treatment as Usual (TAU) Group:
Participants randomized to the treatment-as-usual group will complete a total of 4 visits during Weeks 3 and 4 where they will receive esketamine. At these visits they will also check-in with the study staff and will complete various cognitive assessments and mental health questionnaires. The participant will complete clinician-administered and self-rated scales, and cognitive assessments during Visit 3a (first visit of Week 3) and Visit 5a / Phase 1 End-of-Treatment Visit (Week 5) (see Table 1 for list of assessments to be documented). Esketamine will be administered on Visits 3a, 3c, 4a, and 4c during Weeks 3-4. Participants in this group will not have study visits 3b, 3d, 4b, and 4d (see Table 1).

Following the overlap period between Phases 1 and 2 during Weeks 3 and 4, and the Phase 1 EOT visit (between Weeks 4 and 5), the TAU group will continue with the rest of Phase 2. During this 14-week period (Weeks 5-18), patients in the TAU group will have every-other-week visits during which Patient Reported Outcomes (PROs) and clinician-administered assessments will be recorded (see table 2). On the last visit of Phase 2, the Week 18 visit (EOT Phase 2 Visit), the Emotional Stroop, Emotional N-

back, 3PRLT, RRS, SoCT and CTAS assessments will be recorded in addition to the assessments conducted every-other-week during weeks 5-17. The Emotional Stroop, Emotional N-back, and 3-Option Probabilistic Reversal Learning Task are computer-administered cognitive assessments that measures cognitive control and flexibility. Following the Phase 2 EOT Visit on Week 18, the participant will enter the Phase 3 follow-up period.

Cognitive Behavioral Therapy (CBT) Group:

Participants randomized to the CBT group will complete 8 visits during Weeks 3 and 4. The CBT group will complete the same PROs and clinician-administered assessments as the TAU group on Visits 3a and 5, and they will also be administered esketamine on Visits 3a, 3c, 4a, and 4c during the Week 3/Week 4 period. Four additional visits, in comparison to the TAU group, will be completed on during Weeks 3 and 4. On Visits 3b, 3d, 4b, and 4d, participants will engage in computer-assisted CBT, and during Visits 3b and 4b, they will also complete in-person CBT. The therapy and computer-based CBT may take place virtually.

The initial visit (Visit 3b) will consist of up to 60 minutes of in-person therapist interaction, with subsequent visits being up to 50 minutes. On some CBT visits, following the therapist interaction, subjects will adjourn to a separate room to work alone on the computer program. A research assistant will be present for the initial session to teach the subject how to use the program. Subjects will also have access to the program at home via Internet to use as much or as often as needed. The amount of time spent on the program will be tracked.

Following the overlap period between Phases 1 and 2 during Weeks 3 and 4, and the Phase 1 EOT visit (Week 5a visit), the CBT group will continue with the rest of Phase 2. This 14-week period (Weeks 5-18) will consist of weekly visits for CCBT. During this time, Patient Reported Outcomes (PROs) and clinician-administered assessments will be assessed every two weeks (see table 2). On the last weekly visit of Phase 2, the Week 18 visit (EOT Phase 2 Visit), the Emotional Stroop, Emotional N-back, 3PRLT, RRS, SoCT and CTAS assessments will be recorded in addition to the CBT and the assessments conducted weekly during weeks 5-17. Following the Phase 2 EOT Visit on Week 18, the participant will enter the Phase 3 follow-up period.

5.3 Phase 3: Follow-up

Following completion of Phase 2, all patients will be followed for an additional 8 weeks as part of the Phase 3 follow-up period. Visits will occur every 4 weeks, including the final Week 26 visit, making for a total of two visits. Participants will complete cognitive assessments and mental health questionnaires just as they did during Phase 1 and Phase 2 (see Table 2), however no esketamine or CBT treatment will occur during this

period for either the TAU or CBT group. Each visit will take approximately 1 hour and can be done either in-person or virtually.

Tables 1 and 2 show the schedule of events that each subject will undergo:

Table 1. Schedule of Events, Phase I and First 2 Weeks of Phase II

		PHASE I											
		PHASE II →											
		Wk 1	Wk 1	Wk 1-2	Week 3				Week 4				EOT, Phase I / Week 5 Visit
Task	Screening	V1a	V1b	V1c, V2a, V2b	V3a	V3b	V3c	V3d	V4a	V4b	V4c	V4d	
Study Day	-5-0	1	2	5, 8, 12	15	17	19	21	22	24	26	28	30
Visit Windows		+/- 2 day	+1 day	+/- 2 days	+/- 2 days	+/- 2 days	+/- 3 days	+/- 3 days	+/- 2 days	+/- 2 days	+/- 3 days	+/- 3 days	+/- 2 days
ICF	X												
MINI	X												
ATRQ	X												
Demographics, Medical History	X												
Concomitant Therapies	X	X			X								X
Urine Pregnancy[b]	X												
Review inclusion/ exclusion criteria	X												
Randomization	X												
MADRS		X[e]	X[f]		X[a]								X[a]
BDI		X[e]	X[f]		X								X
BSI		X[e]	X[f]										
CGI		X[e]	X[f]		X[a]								X[a]
3PRLT		X			X								X
Emotional Stroop		X			X								X
Emotional N-back		X			X								X
RRS		X			X								
SoCT		X			X								
CTAS		X			X								
Assessment of AEs		X		X	X				X				X
C-SSRS	X[e]	X[f]	X[f]		X[a]								X[a]
Esketamine		X		X	X		X		X		X		X
GDA[c]						X		X		X		X	X
CBT, in-person[d]						X				X			X

[a]Clinician ratings- For Esketamine, CBT, and TAU visits, preference will be that all scales are administered within a 24-hour period before treatment visits. However, a 24-hour post-visit window will be permitted, so long as participants are not assessed within 6 hours of esketamine.
[b]For females of child-bearing potential, as per clinical site policy
[c]For CBT group only; can be completed on site or remote
[d]For CBT group only
[e] Baseline assessments to be collected within 24 hours of first dose.
[F] Assessments must be done 24-48 hours AFTER the initial Esketamine dose.

Table 2. Schedule of Events, Phases II and III						
	Phase II				Phase III (follow-up phase)	
	Week 5 / Visit 5a / EOT Phase I	Weeks 5-6, V5b, V6a, V6b[a]	Weeks / Visits 7-17[b]	Week / Visit 18 (EOT Phase II)	Week / Visit 22	Week / Visit 26 / End of Study Visit
Study Day	30	33, 36, 40	43-113	120	148	176
Visit Windows	+/- 2 days	+/- 2 days	+/- 2 days	+/- 2 days	+/- 7 days	+/- 7 days
MADRS	X[e]		X[e]	X	X	X
CSSRS	X[e]		X[e]	X	X	X
BDI	X		X	X	X	X
BSI	X		X	X	X	X
CGI	X[e]		X[e]	X	X	X
3PRLT				X		X
Emotional Stroop				X		X
Emotional N-back				X		X
Assessment of AEs	X		X	X	X	X
Concomitant Therapies	X		X	X	X	X
RRS			X[f]	X		X
SoCT			X[f]	X		X
CTAS			X[f]	X		X
GDA[c]	X	X	X			
CBT in-person[d]	X	X	X			

[a]Visits 5b, 6a, and 6b during Weeks 5-6 are only applicable to the CBT group
[b]During Visits/Weeks 7-17, subjects in the CBT group will have weekly visits to engage in CBT. Subjects in the TAU group will have visits every other week (on the odd weeks). During Weeks/Visits 7-17, all assessments will be done every other week on the odd weeks.
[c]For CBT group only; can be completed on site or remote
[d]Only the group randomized to CBT will receive CBT;
[e]Clinician ratings- For Esketamine, CBT, and TAU visits, preference will be that all scales are administered within a 24-hour period before treatment visits. However, a 24-hour post-visit window will be permitted, so long as participants are not assessed within 6 hours of esketamine.
[f] The RRS and the SoCT and CTAS are completed at week 11 only.

6. CONCOMITANT MEDICATION AND THERAPIES

6.1 Medications and Therapies Allowed During Study:

Patients will be allowed to continue their existing psychotropic medications. Changes in psychotropic medications throughout the trial are best avoided but are permitted according to investigator discretion. These medications must be recorded on the Psychiatric Medication Log.

Subjects should continue medications for other conditions and be reminded to tell study staff of any changes to medical history or concomitant medications. This will be assessed at each visit prior to treatment. All subjects should receive optimal care for any side effects occurring during the study (nausea, headache, etc.) according to local standards of care or evidence-based guidelines, and at the discretion of the investigator.

6.2 Prohibited Medications and Therapies:

Participants in the TAU group should not be enrolled in the study if they are receiving or plan to receive formalized CBT psychotherapy focused on treatment of their mood disorder/suicidal ideation during the study. For the purposes of this study, CBT will be operationalized to include participation at an Intensive Outpatient Program (IOP) which runs a formal CBT-based program or participation with a one-on-one therapist who follows a formal CBT protocol as defined by the following characteristics; each session has an agenda, a homework assignment is given at each sessions, and each session reviews the homework assignment from the previous session. Inpatient group therapy and non-CBT-based IOP is permitted. Changes in medical history and concomitant medications/therapies will be assessed throughout the study, and patients in the TAU group may be withdrawn from the study at any point if they begin formalized CBT psychotherapy.

7. STUDY PROCEDURES

7.1 Screening / Intake Visit

It is estimated the screening intake will take approximately 2 hours. It will consist of the following procedures and assessments and can be completed in up to 5 days:

a. Informed Consent: A delegated study team member will discuss risks and benefits of participation and review the study overview with the patient. The patient will sign the informed consent form prior to any study procedures being performed.
b. Clinical and Demographic Intake (including medical and psychiatric history, medication history, and current medications)
    i. Mini International Neuropsychiatric Interview (MINI) and Diagnostic Interview
    ii. Antidepressant Treatment Response Questionnaire (ATRQ) and current Medication Log
    iii. Columbia Suicide Severity Rating Scale (CSSRS) [this screening assessment does not need to be completed by central/remote rater]
c. Urine pregnancy test for females of child bearing potential per site clinical policy
d. Review of Inclusion/Exclusion Criteria by investigator

Following screening, participants may begin clinical treatment with esketamine later that same day or up to 5 days later.

7.2 Randomization of Participants

Randomization can be done by study staff after the screening visit and after exclusion/inclusion criteria have been reviewed and it is confirmed subject is eligible. All eligible patients will be randomized in a 1:1 ratio to receive either CBT plus TAU or TAU alone following standard of care esketamine treatment. The randomization will take

place after screening before Eskatamine treatment begins. Given the nature of these treatments, treatment arms cannot be blinded at the patient level. Raters (for some clinician-administered scale, such as the MADRS) will remain blinded. Randomization will be conducted centrally through a secure electronic data management system and will be stratified by site.

7.3 Screen Failures:

If the patient fails to qualify for the study after signing the informed consent form, they will be considered a screen failure. Patients who screen fail or who do not complete the study after randomization will not be eligible for future enrollment.

7.4 Baseline/Visit 1a

This visit will occur on the day of the first treatment with esketamine. All assessments should be done before dosing except for the MADRS, CGI, CSSRS, BDI and BSI. These assessments will be completed 24-48 hours post the first Esketamine treatment. The esketamine treatment is done per standard clinical care. It is anticipated that the assessments for this visit will take approximately 1.5 hours, not including the administration of esketamine. Baseline/Visit 1a assessments include the following (which should be completed within 24 hours prior to first esketamine dose:

a. Clinician-administered assessments:
    i. MADRS (central/remote rater)
    ii. CGI
    iii. CSSRS (central/remote rater)
    iv. Assessment of AEs
    v. Concomitant Therapies
b. Patient-Reported Outcomes:
    i. BDI
    ii. BSI
    iii. RRS
    iv. SoCT
    v. CTAS
c. Cognitive Assessments:
    i. 3PRLT
    ii. Emotional Stroop
    iii. Emotional N-back
d. Treatment (clinical care, not part of research):
    i. Esketamine (84mg)

7.5 Visit 1b (24-48 hour assessment)

This visit consists only of assessments:

e. Clinician-administered assessments:
    vi. MADRS (central/remote rater)
    vii. CSSRS (central/remote rater)
f. Patient-Reported Outcomes:
    vi. BDI
    vii. BSI

7.6 Visits 1c, 2a, and 2b (Weeks 1-2)

Visits 1b, 2a, and 2b occur on days that the subject receives esketamine treatment. Altogether, Visits 1a-2b occur over a 2-week period (plus or minus 1 week window), with 2 visits per week. These visits only consist of esketamine, which is the clinical care and not part of the research:

a. Treatment (clinical care, not part of research):
    i. Esketamine (84mg, or lowered dose at the discretion of the study clinician)

7.7 Visit 3a (Week 3)

Following 4 total esketamine treatments, Phase 2 will begin (Visit 3a, which will typically be Week 3). During this Phase, half of participants begin CBT. Visit 3a is comprised of the following assessments.

a. Clinician-administered assessments:
    i. MADRS (central/remote rater; minus 2-day window)
    ii. CGI (minus 2-day window)
    iii. CSSRS (central/remote rater; minus 2-day window)
    iv. Assessment of AEs
    v. Concomitant Therapies
b. Patient-Reported Outcomes:
    i. BDI
    ii. BSI
c. Cognitive Assessments:
    i. 3PRLT
    ii. Emotional Stroop
    iii. Emotional N-back
    iv. RRS
    v. SoCT
    vi. CTAS
d. Treatment (clinical care, not part of research):
e. Esketamine (84mg, or lowered dose at the discretion of the study clinician)

7.8 Visit 3b, 3d, 4b, and 4d (Weeks 3, 4; CBT group only)

These visits only occur for the CBT group. These can be done virtually or in-person. They include only the CBT procedure, which is a combination of in-person and computer-assisted CBT.

a. Study Treatments:
    i. In-person and/or GDA computer-assisted CBT (Esk+CBT group only)

7.9 Visit 3c, 4a, and 4c (Weeks 3, 4)

These visits are comprised of esketamine treatments.

a. Esketamine Treatments:
    i. Esketamine (84mg, or lowered dose at the discretion of the study clinician)

7.10 Phase 1 EOT Visit / Visit 5a (Week 5)

The Phase 1 EOT Visit / Visit 5a consists of clinician-administered, patient-reported outcomes, and cognitive assessments. This visit should take approximately 1.5 hours (not including CBT):

a. Clinician-administered assessments:
    i. MADRS (central/remote rater; minus 2-day window)
    ii. CGI (minus 2-day window)
    iii. CSSRS (central/remote rater; minus 2-day window)
    iv. Assessment of AEs
    v. Concomitant Therapies
b. Participant-rated Scales:
    i. BDI
    ii. BSI

c. Cognitive Assessments:
    i. 3PRLT
    ii. Emotional Stroop
    iii. Emotional N-back
d. Study Treatments:
    i. In-person and/or GDA computer-assisted CBT (CBT group only)

7.11 Visits 5b, 6a, 6b (Weeks 5, 6; CBT group only)

These visits are comprised of a combination of in-person and computer-assisted CBT. These visits do not occur for the TAU group.

a. Study Treatments:

i. In-person and/or GDA computer-assisted CBT (CBT group only)

7.12 Visits 7-17 (Weeks 7-17)

For Visits 7-17, the CBT group will have weekly visits with CBT. The TAU group will have visits every other week (on the odd weeks). For the assessments (not including CBT times), it is anticipated these visits will last approximately 30-45 minutes. The following assessments and procedures will be completed on odd weeks only (7, 9, 11, 13, 15, 17):

a. Clinician-administered assessments:
    i. MADRS (central/remote rater; minus 2-day window)
    ii. CGI (minus 2-day window)
    iii. CSSRS (central/remote rater; minus 2-day window)
    iv. Assessment of AEs
    v. Concomitant Therapies
b. Participant-rated Scales:
    i. BDI
    ii. BSI
    iii. SoCT (Week / Visit 11 only)
    iv. CTAS (Week / Visit 11 only)
    v. RRS (Week / Visit 11 only)
c. Study Treatments:
    i. In-person and/or GDA computer-assisted CBT (CBT group only)

7.13 Phase 2 EOT Visit / Visit 18 (Week 18)

Visit 18 marks the EOT Visit for Phase 2. The following assessments and procedures will be completed at this visit, which will take approximately 1.5 hours (excluding CBT time):

a. Clinician-administered Scales/Assessments:
    i. MADRS (central/remote rater; minus 2-day window)
    ii. CGI (central/remote rater; minus 2-day window)
    iii. CSSRS (central/remote rater; minus 2-day window)
    iv. Assessment of AEs
    v. Concomitant Therapies
b. Participant-rated Scales:
    i. BDI
    ii. BSI
    iii. RRS
    iv. SoCT
    v. CTAS
c. Cognitive Assessments:
    i. 3PRLT

ii. Emotional Stroop
iii. Emotional N-back

d. Study Treatments:
i. CBT (CBT group only)

7.14 Visit 22 / Week 22 (Phase 3 - Follow-up) – approximately 1 hour

a. Clinician-administered Scales/Assessments (central/remote rater):
i. MADRS (central/remote rater; minus 2-day window)
ii. CGI (minus 2-day window)
iii. CSSRS (central/remote rater; minus 2-day window)
iv. Assessment of AEs
v. Concomitant Therapies

b. Participant-rated Scales:
i. BDI
ii. BSI

7.15 End-of-Study Visit / Visit 26 (Week 26)

a. Clinician-administered Scales/Assessments:
i. MADRS (central/remote rater; minus 2-day window)
ii. CGI (minus 2-day window)
iii. CSSRS (central/remote rater; minus 2-day window)
iv. Assessment of AEs
v. Concomitant Therapies

b. Participant-rated Scales:
i. BDI
ii. BSI
iii. RRS
iv. SoCT
v. CTAS

c. Cognitive Assessments:
i. 3PRLT
ii. Emotional Stroop
iii. Emotional N-back

8. NON-COMPLIANCE

A patient can be withdrawn from the study for non-compliance, per investigator discretion, if they miss several consecutive study visits.

9. SUBJECT WITHDRAWAL

Subjects may withdraw from study participation or from the study treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits. If the subject elects to discontinue participation in the study or to discontinue study treatment, the investigator should:

- Inquire about the reason for withdrawal
- Request the subject to return for an EOT Visit to assess AEs/SAEs, safety endpoints, outcome events, vital status
- Follow-up with the subject regarding any unresolved adverse events. Any unresolved events at study end of withdrawal should be followed for 2 weeks, until resolution, or until an adequate treatment plan is in place.

If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Adequate documentation of this request should be obtained and retained in the subject's source file. True withdrawal of consent should be initiated by the subject and in writing. Data collected before withdrawal of consent may be retained and used for analysis.

10. LOST TO FOLLOW-UP

Contact information from the patient, including an emergency contact will be obtained at the time of screening.

Patients will be considered lost to follow-up after three attempts to contact. Study staff will document the attempts to contact in the research chart. Every attempt should be made to contact the patient as soon as possible after a missed visit. The site should access medical records and contact the participant' health care professional(s) to contact the patient. The patient's vital status should be obtained, if possible, at the time of the end of study (Week 26) from a reliable source or from medical records.

11. STUDY TERMINATION

This study may be terminated or suspended at any time. If the study is terminated or suspended participating institutions will be notified. The central IRB will be promptly informed and provided the reasons(s) for the termination or suspension, as specified by the applicable regulatory requirement(s).

12. SAFETY MONITORING AND REPORTING

12.1 Adverse Events

Patients will be closely monitored for adverse events (AEs) including worsening of depression symptoms. An adverse event will be defined as any untoward medical occurrence associated with the use of a therapy, whether or not considered therapy related. Study investigators will be able to modify treatment or remove patients from the trial based on their clinical discretion and specific patient outcomes. Assessment of adverse events, including grading of severity and attribution to research will start at the time of consent. AEs will be evaluated throughout the study and recorded on the appropriate CRF.

The following adverse events will be collected from the time of randomization for the study:

Adverse events that are not listed in the current labeling for esketamine or GDA. This includes events that are similar to those on the labeling but differ from the event because of greater severity or specificity.

- The following AEs will be considered of special interest:
- Suicide Attempt
- Non-suicidal self-injury

Standard Adverse Event (AE) reporting will be collected weekly during Phase I.

Study Treatment Discontinuation Adverse Events

Events that lead to the discontinuation of esketamine during Phase 1, and events leading to the discontinuation of in-person CBT or the GDA program during Phase 2 will be collected for the study. These events will be recorded on either an AE or an SAE form.

Serious Adverse Events

Patients will be closely monitored for serious adverse events (SAEs). Study investigators will be able to modify treatment or remove patients from the trial based on their clinical discretion and specific patient outcomes.

All SAEs that meet the following definition will be collected from the time of consent until completion of the Phase 3 EOS Visit (Week 26):

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Documentation and Reporting of Serious Adverse Events

SAEs will be reported to the Project Manager within 24hours of becoming aware of the event. Participating site teams will report the event to WIRB or their local IRB as per their reporting policies. The causality of the SAE (the relationship to the study treatment/procedures) will be assessed by the local investigator and reviewed by the Sponsor Investigator. SAEs that are unexpected and deemed to be related or possibly related by the Sponsor Investigator will be submitted for review by the DSMB within 10 days of initial report to the sponsor. These reviews can occur via email or at a convened DSMB meeting. The DSMB will evaluate the SAE and can make recommendations to modify the research plan if necessary. The SAE will also be documented on the appropriate eCRF.

Pregnancy

All pregnancies should be reported to the appropriate regulatory authorities and IRBs as per their reporting policy.

- Maternal exposure – If a patient becomes pregnant during the course of the study during which the participant is receiving esketamine (Phase 1), esketamine treatment will be discontinued per investigator discretion.
- Paternal exposure – There are no known risks regarding fathering a child while receiving esketamine treatment or CBT, but since there is limited data on esketamine in pregnancy it is advised that subjects practice adequate birth control while in the study.

13. STATISTICAL PLAN

The key exposures of this study are esketamine treatment during Phase 1 and CBT (computer-based and in-person) during Phase 1/2. The primary aims of this study are to 1) determine the feasibility and safety of performing a larger study with similar design and 2) to evaluate the appropriateness and utility of the proposed tests of cognitive control measures in exploring the mechanisms of change. However, some statistical analyses will also be performed to generate preliminary data on the efficacy of esketamine/CBT combination compared to esketamine/TAU in reducing the risk of suicide.

A between-group comparison on suicidal ideation measured throughout the trial. In specific, we will conduct a general, linear mixed-model analysis of suicidal ideation, as measured by item 10 of the MADRS. Based on a sample size of 60 patients, assuming a one-sided alpha of 0.05 (based on industry standards for a feasibility/Phase 2 study), we would be able to detect a large-to-medium effect size of CBT on this measure (Cohen's d~0.6).

Additional measures will include the BSI as well as counts of rehospitalization and suicide attempts (as measured by the CSSRS).

14. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be appointed to monitor the key safety and efficacy outcomes at regular intervals, to safeguard the safety and interests of the study participants and maintain/uphold the scientific merit of the study. Members of the DSMB will not be investigators of the study. The DSMB Charter document will guide the conduct of the DSMB and will include the procedures and stopping rules for the study.

Study progress reports will be presented at regular intervals to the Data and Safety Monitoring Board (DSMB), to the NIH, and to the study investigators.

15. DATA HANDLING AND RECORD KEEPING

15.1 Data Collection

All data collection and data entry will be performed by site research staff. Data sources include patient reports, clinician and participant-rated assessments, cognitive assessments, and available medical records. The primary mode of data collection will be directly onto source documentation. After ensuring data is accurate and complete, data will then be entered into electronic case report forms (eCRF) (using REDCap), through a device that is encrypted and secured according to site institutional standards for information security. YCCI will also provide equivalent paper forms, for use in situations where a suitably secure, internet-connected device is unavailable (e.g., an interview conducted after hours at home). Staff will be trained in the proper handling of paper forms.

Additionally, an eCRF must be completed for each consented patient. It is the responsibility of the Investigator to ensure that the eCRF is completed accurately and in a timely manner. Screen failures should be recorded on the electronic screen failure log with the reason for ineligibility.

15.2 Retention of Records

The Investigators must maintain all confidential study documentation and take measures to prevent accidental or premature destruction of these documents. Documents should be retained for a minimum of 7 years after the completion or discontinuation of the clinical trial. However, applicable regulatory and institutional requirements will be taken into account in the event that a longer period is required.

16. STUDY MONITORING, AUDITING, AND INSPECTING

Study site monitoring is necessary to assure adequate protection of the rights of human subjects and the safety of all subjects involved in clinical investigations and the quality and integrity of the resulting data submitted. The study will be monitored according to the Monitoring Plan.

The Study Principal Investigator-designated monitor(s) conducts monitoring visits to ensure that clinical investigators and study team members are compliant with the protocol, ICH good clinical practice, federal, state and local regulations and institutional policies and procedures, that data are of high quality and integrity, and that the facilities and staffing are adequate for continued study participation. This will be performed by conducting monitoring visits including a site initiation visit, regularly scheduled interim monitoring visits and/or remote interim monitoring visits while subjects are on study, and a site close-out visit at all participating sites. Following each site visit, a visit report will be generated containing information on site activities and a summary of pertinent points and action items. The report will be provided with a follow-up letter. Site-specific data status reports will be distributed to the site regularly to outline planned, missing or incomplete case report forms and any outstanding data queries.

During monitoring visits, the following may be reviewed:

- Protection of the rights, safety and welfare of subjects through review of informed consent process and documentation, adverse events (AEs) and serious adverse events (SAEs) and safety procedures
- Subject eligibility
- Source verification
- Protocol compliance
- Deviations and Non-compliance
- Investigator Site File
- GCP compliance
- Esketamine administration
- Additional study supplies inventory and assessment
- Study progress and/or follow-up on issues with Site Principal Investigator (PI) and relevant members of the study team

The Study PI and YCCI will define the required study monitoring activities in a Study Monitoring Plan.

17. ETHICAL CONSIDERATIONS

The study protocol, consent forms, and recruitment materials will be submitted to a central IRB (Western Investigational Review Board/WIRB). All study personnel will have completed training in Good Clinical Practice and maintain evidence of completion in the Investigator Site File.
This study will be among the first NIH-funded trials to recruit patients who are specifically at imminent risk of suicide by virtue of their presentation to emergency department settings or inpatient units. It is our hope that we can demonstrate the safety and feasibility of collecting high quality data from this population, so that we will have the opportunity to make a significant contribution to the knowledge base of how to treat this very high-risk population following hospital discharge.

17.1 Central Institutional Review Board (IRB)

It is the investigator's responsibility to ensure that the study protocol and informed consent documents are reviewed and approved by WIRB.

If, during the study, it is necessary to amend either the protocol or informed consent document, the investigator will be responsible for ensuring that the WIRB reviews and approves the amended documents. WIRB approval of any procedures must be obtained before implementing new processes or procedures.

17.2 Informed Consent Document and Process

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision. The informed consent document will inform patients of their right to refuse any release of their protected health information.

The investigator or his/her designee (i.e., research coordinator or study nurse) will inform the patient of all aspects of the study pertaining to the patient's participation in it. The process for obtaining informed consent will be in accordance with all applicable regulatory requirements and completed by a trained research staff member. The informed consent form (ICF) must be signed and dated by the patient and the investigator or his/her designee BEFORE the patient can participate in the study. The participant will receive a copy of all signed and dated documents, and the originals will be retained in the patient's study file and/or medical record. The consent process will be documented and maintained.

17.3 Subject Information and Consent

Each clinical site is responsible for the confidentiality of the data associated with participants enrolled in this study, in the same manner that it is responsible for the confidentiality of any patient information within its sphere of responsibility. All forms used for the study data will be identified by coded identification number, which will be generated at the clinical center, by registering the participant into REDCap, to maintain subject confidentiality. Only the minimum necessary protected health information will be indicated on the forms. All hard-copy study records will be kept in a locked office in locked file cabinets at the clinical centers with access limited to study staff, and all study staff will identify participants via their unique identifier. All digital study forms and data will be kept on secure, password-protected data management program called REDCap.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the DSMB or WIRB. The participant grants permission to share research data with these entities in the consent document. Federal regulations govern the protection of patient's rights relative to data confidentiality and use of research data.

18. PUBLICATION AND DISCLOSURE

The study findings will be disseminated to the public through manuscripts, scientific and patient organization led conferences, press releases and through a dedicated website. The PIs may also publicize the study findings through talks and public symposia with their local mental health advocacy organizations (NAMI, DBSA, etc.).

This study will be registered on ClinicalTrials.gov.

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