

Protocol S-25-01

A Randomized, Double-Blind, Active-Controlled, Clinical Trial of the Safety, Efficacy, and Durability of MDMA-Assisted Therapy for Military Service Members with Posttraumatic Stress Disorder

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Protocol Amendment Summary of Changes

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List of Abbreviations

Abbreviation	Definition
°C	Degrees Celsius
°F	Fahrenheit
5HT	Serotonin
ACE	Adverse Childhood Experiences Questionnaire
ACT	Acceptance and Commitment Therapy
AD	Active Duty
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
API	Active Pharmaceutical Ingredient
AR	Army Regulation
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BAMHT	Beliefs About Mental Health Treatment
BDI-II	Beck Depression Inventory-II
BETS	Blast Exposure Threshold Survey
bHCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
BMP	Basic Metabolic Panel
BPM	Beats per Minute
BUN	Blood Urea Nitrogen
CAM	Confusion Assessment Method
CAPS-5-R	Revised Clinician-Administered PTSD Scale for DSM-5
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CPT	Cognitive Processing Therapy
CRA	Clinical Research Associate
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP2D6	Cytochrome P450 2D6
DCAC	Data Coordinating and Analysis Center
DEA	Drug Enforcement Administration

Abbreviation	Definition
DEG	Differentially Expressed Gene
DHA R&D - MRDC	Defense Health Agency Research & Development - Medical Research & Development Command
DMP	Data Management and Sharing Plan
DoD	Departmeant of Defense
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision
DUDIT	Drug Abuse Disorders Identification Test
DUDIQ	Drug Use Desire and Intent Questionnaire
DUQ	Drug Use Questionnaire
EA	Euphoria Assessment
EASI	Endorsed and Anticipated Stigma inventory
EKG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
EEG	Electroencephalography
EMS	Emergency Medical Services
ER	Emergency Room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
HIPAA	Health Insurance Portability and Accountability
HIT-6	Headache Impact Test 6
HJF	Henry M. Jackson Foundation
HLA	Human Leukocyte Antigen
HPQSF	Health and Work Performance Absenteeism and Presenteeism Short Form
ICD	International Classification of Disease
ICF	Informed Consent Form
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
IND	Investigational New Drug
INQ-15	15-item Interpersonal Needs Questionnaire
INR	International Normalized Ratio

Abbreviation	Definition
IR	Independent Rater
IRB	Institutional Review Board
IRR	Interrater Reliability
ISM	Independent Safety Monitor
IUD	Intrauterine Device
kg	Kilogram
LEC-5	Life Events Checklist
LSD	Lysergic Acid Diethylamide
LSL	LabStreamingLayer
MAPS	Multidisciplinary Association for Psychedelic Studies
MAOI	Monoamine Oxidase Inhibitor
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDA	3,4-Methylenedioxyamphetamine
mDEQ-3	Modified Drug Effects Questionnaire–3
MDMA	midomafetamine or 3,4-methylenedioxymethamphetamine
MDMA-AT	MDMA assisted therapy
mg	Milligram
MHS	Military Health System
MIOS	Moral Injury Outcome Scale
mITT	Modified Intent-to-Treat
MINI	Mini International Neuropsychiatric Interview
mmHg	Milligrams of Mercury
MMRM	Mixed Model Repeated Measure
MPFI-24	Multidimensional Psychological Flexibility Inventory-24
MRO	Medical Review Officer
ms	Millisecond
MSPSS	Multidimensional Scale of Perceived Social Support
MT	Medication Taper Phone Call
MTF	Medical Treatment Facilities
NDA	New Drug Application
NDAA	National Defense Authorization Act
NIH	National Institutes of Health
NP	Nurse Practitioner
NSAB	Naval Support Activity Bethesda

Abbreviation	Definition
OHARO	Office of Human and Animal Research Oversight
OHRO	Office of Human Research Oversight
ORA	Office of Regulated Activities
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method
PA	Physician's Assistant
PCL-5	PTSD Checklist for DSM-5
PE	Prolonged Exposure
PEG	Pain, Enjoyment of Life and General Activity Scale
PGx	Pharmacogenomics
PI	Principal Investigator
PIES	Perceived Invalidation of Emotion Scale
PMDB-M	Prevention and Management of Disruptive Behavior-Military
POC	Point-of-Care
PPS	Psychedelic Preparedness Scale
PSQI	Pittsburgh Sleep Q654uality Index
PSRT	Protocol Safety Review Team
PSSO	Product Safety Surveillance Office
PTSD	Posttraumatic Stress Disorder
PVC	Premature Ventricular Contractions
qPCR	Quantitative Polymerase Chain Reaction
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
RTM	Reactions to Touch Measure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCI	Sensitive Compartmented Information
SCID-5-PD	Structured Clinical Interview for DSM-5 Personality Disorders
SCID-5-SPQ	SCID-5 Self-report Personality Questionnaire
SCS	Self-Compassion Scale
SCS-SF	Self-Compassion Scale-Short Form
SERT	Serotonin Reuptake Inhibitor
SETS	Stanford Expectations of Treatment Scale
SM	Service Member
SNP	Single Nucleotide Polymorphism
SOCOM	Special Operations Command
SR	Shame-Related

Abbreviation	Definition
SSRI	Selective serotonin reuptake inhibitor
STUQ	Smoking and Tobacco Use Questionnaire
TBI	Traumatic Brain Injury
TEAE	Treatment Emergent Adverse Event
TFA	Theoretical Framework of Acceptability
TLFB	Timeline Follow-Back Calendar
TMC	Training Monitoring Committee
TPN	Total Parenteral Nutrition
TSH	Thyroid-stimulating Hormone
ULN	Upper Limit of Normal
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
U.S.	United States
USAMRDC	United States Army Medical Research and Development Command
VA	Department of Veterans Affairs
VAS	Visual Analog Scale
VHD	Valvular Heart Disease
WAI-SR	Working Alliance Inventory-Short Revised
WHODAS	World Health Organization Disability Assessment Schedule
WHOQOL-BREF	World Health Organization Quality of Life - BREF
WRNMMC	Walter Reed National Military Medical Center

1 Protocol Summary

1.1 Synopsis

1.1.1 Protocol Title

A Randomized, Double-Blind, Active-Controlled, Clinical Trial of the Safety, Efficacy, and Durability of MDMA-Assisted Therapy for Military Service Members with Posttraumatic Stress Disorder

1.2 Rationale

Posttraumatic stress disorder (PTSD) is the most common psychiatric cause of medical discharges from the military.[1] Current gold-standard treatments such as Prolonged Exposure and Cognitive Processing Therapy lead to 28-40% of participants no longer meeting PTSD diagnostic criteria, with approximately 40% dropping out of treatment.[2] Whereas, in Phase 3 clinical trials of MDMA-AT (MDMA[midomafetamine]-assisted therapy), 67-71% no longer meet PTSD diagnostic criteria, with moderate to large effect sizes (Cohen's d = 0.7-0.91, between-group; d = 1.4-2.1, within-group), and less than 10% drop out despite the longer course of treatment.[1,3,4] Improvements in PTSD symptoms also appear to be durable up to 1 and nearly 4 years after completing a course of MDMA-AT.[1] There is a significant unmet need necessitating a new paradigm for treating military Service Members (SMs) with PTSD. However, evidence of MDMA-AT for SMs with PTSD does not yet exist. Section 723 of the 2024 National Defense Authorization Act (NDAA) authorized the Department of Defense (DoD) to fund and study MDMA-AT in SMs, and this study is directly supported by this NDAA 2024 authorization.[5] Not only does this study aim to address many of the most critical unanswered questions for offering MDMA-AT to a military population, but it also is designed to address many of the gaps recently identified by the Food and Drug Administration's (FDA's) review of the first New Drug Application (NDA) for MDMA-AT in 2024. This study will accomplish these aims by 1) evaluating the clinical and operational impacts of MDMA-AT in SMs and 2) informing potential post-FDA-approval clinical implementation of MDMA-AT within the Military Health System (MHS).

1.3 Protocol Objectives and Endpoints

1.3.1 Objectives

The overall objective for the study is to determine the safety, efficacy, and durability of delivering MDMA-AT through a Simultaneous Dosing Model for military SMs to reduce symptoms of PTSD and associated comorbidities, as compared to the same therapy combined with low-dose MDMA.

1.3.2 Primary Objective

The primary objective of this study is to determine treatment efficacy of MDMA-AT for PTSD by comparing between-group changes in PTSD symptom severity as measured by independent raters with the CAPS-5-R (Revised Clinician-Administered PTSD Scale for DSM-5) from baseline to the primary endpoint at 1 month after the third dosing session.

1.3.3 Secondary Objectives

1. Determine durability of treatment efficacy by comparing between-group changes in PTSD symptom severity (Revised Clinician-Administered PTSD Scale for DSM-5 [CAPS-5-R]), from primary endpoint to secondary endpoint.
2. Determine between-group differences in functional disability (World Health Organization Disability Assessment Schedule [WHODAS] 2.0) from baseline to primary endpoint.
3. Determine durability of between-group differences in functional disability (WHODAS 2.0) between primary endpoint and secondary endpoint.
4. Describe the number of simultaneously overlapping Support Events (when a study team member enters the dosing room to provide assistance) per study arm and combined overall.

1.3.4 Safety Objectives

The overall safety objective is to assess differences between groups in cardiac and cardiovascular safety; vital signs; hepatic functioning; impact on key electrolytes; severity, incidence and frequency of Adverse Events (AEs), Treatment Emergent Adverse Events (TEAEs), Adverse Events of Special Interest (AESIs), and Serious Adverse Events (SAEs); suicidal ideation and behavior; illicit substance use; and incidence, severity, and duration of Support Events. The following safety objectives will evaluate the safety of full-dose MDMA-assisted therapy compared to identical therapy with low-dose MDMA:

1. Describe change in ΔQTcMax (QTc at 2 hours and 4 hours post-dosing versus baseline per Holter monitor electrocardiogram [EKG]) for each dosing session by initial doses of 40, 80, and 120 mg of MDMA.
2. Describe the frequency of events of ΔQTcMax > 60 ms (per Holter monitor EKG) for each dosing session by initial doses of 40, 80, and 120 mg of MDMA.
3. Describe the frequency of events of QTcMax > 500 ms (per Holter monitor EKG) for each dosing session by initial doses of 40, 80, and 120 mg of MDMA.
4. Describe the frequency of arrhythmias identified via Holter monitor EKG during each dosing session by initial doses of 40, 80, and 120 mg of MDMA.
5. Describe changes in vital signs (blood pressure, heart rate, and body temperature) from pre-Investigational Product (IP) administration to 2 hours post-dosing, 4 hours post-dosing, and end of each Dosing Session by initial doses of 40, 80, and 120 mg of MDMA.
6. Describe hepatic functioning before and after each Dosing Session by initial doses of 40, 80, and 120 mg of MDMA, as measured by alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), and total/direct/indirect bilirubin.
7. Describe the frequency of meeting drug-induced liver injury stopping criteria after Dosing Sessions by initial doses of 40, 80, and 120 mg of MDMA, as measured by ALT, AST, ALP, and total/direct/indirect bilirubin.
8. Describe the frequency of meeting close observation for liver injury criteria after Dosing Sessions by initial doses of 40, 80, and 120 mg of MDMA, as measured by ALT and AST.
9. Describe the frequency of disposition outcomes (continued enrollment vs study withdrawal) after meeting close observation for liver injury criteria after Dosing Sessions by initial doses of 40, 80, and 120 mg of MDMA.

10. Describe sodium and potassium levels before and after each Dosing Session by initial doses of 40, 80, and 120 mg of MDMA.
11. Describe the frequency of AEs by maximum severity across both study arms as well as during and after each Dosing Session by initial doses of 40, 80, and 120 mg of MDMA.
12. Describe the frequency of AEs by maximum severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, continuing at primary endpoint, or continuing at secondary endpoint by treatment arm.
13. Describe the frequency of TEAEs by relation to IP in the full-dose vs low-dose MDMA arms.
14. Describe the frequency of TEAEs by maximum severity reported during a Dosing Session and at each Integration Session in the full-dose vs low-dose MDMA arms.
15. Describe the frequency of SAEs in the full-dose vs low-dose MDMA arms
16. Describe the frequency of positive or serious ideation and suicidal behavior in the full-dose vs low-dose MDMA arms, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS).
17. Describe the frequency of illicit substance use in the full-dose vs low-dose MDMA arms, as measured by the Drug Use Questionnaire (DUQ).
18. Describe the number of simultaneous Support Events per study arm and combined overall, and by minimum Monitor training level required per event.
19. Describe the number and nature of simultaneous dosing Support Events categorized as Emergent, Urgent, or Routine Therapist events and Emergent, Urgent, or Routine Participant events.
20. Describe time between therapist-initiated Support Event requests and the supporting Monitor entering the room.
21. Describe the number of Support Events that required ≤ 5 minutes and > 5 minutes for the supporting Monitor to enter the room by treatment arm.
22. Characterize reported barriers to a quicker response for each Support Event that took > 5 minutes for the supporting Monitor to enter the room as well for all Support Events overall.
23. Characterize frequency and duration of Support Events per study arm and overall.
24. Characterize what qualitative interventions, if any, were provided by the supporting Monitor during a Support Event by treatment arm.
25. Assess the feasibility of a Non-clinical Assistant Monitor temporarily monitoring participants for low-risk Support Events by characterizing any corresponding AEs during these events.
26. Assess the feasibility of a Non-clinical Assistant Monitor temporarily monitoring participants for low-risk Support Events by evaluating the frequency of a Clinical Assistant Monitor or Supervising Monitor needing to enter the room during these Support Events.
27. Describe the frequency of meeting modified CAM discharge criteria at the planned end of the dosing session in the full-dose vs low-dose MDMA arms.
28. Describe the time from planned end of dosing session to discharge in the full-dose vs low-dose MDMA arms.
29. Describe the discharge criteria not met at the planned end of dosing session in the full-dose vs low-dose MDMA arms.
30.

1.3.5 Exploratory Objectives

1. Describe rates of response, loss of diagnosis, and remission of PTSD symptoms compared between groups from baseline to primary and secondary endpoints, as measured by changes in CAPS-5-R scores.
2. Compare PTSD severity (PTSD Checklist for DSM-5 [PCL-5]) after each Dosing Session between groups.
3. Describe treatment tolerability as measured by rates of dropout due to AE intolerability throughout study period by group.
4. Assess treatment acceptability using acceptability scores from the Theoretical Framework of Acceptability (TFA) questionnaire conducted during the follow-up phase in the treatment group.
5. Analyze participants' qualitative experiences and feedback (Qualitative Interview).
6. Evaluate between-group differences in the following domains between baseline and primary endpoint as well as durability of differences between primary and secondary endpoint:
    a. Comorbid depression (Beck Depression Inventory-II [BDI-II])
    b. Suicidality (C-SSRS)
    c. Sleep disturbance (Pittsburgh Sleep Quality Index [PSQI])
    d. Moral injury (Moral Injury Outcome Scale [MIOS])
    e. Quality of life (World Health Organization Quality of Life-BREF [WHOQOL-BREF])
    f. Burden of absenteeism and presenteeism (Health and Work Performance Absenteeism and Presenteeism Short Form [HPQSF])
    g. Alcohol use (Timeline Follow-Back Calendar, Alcohol [TLFB])
    h. Nicotine use (Smoking and Tobacco Use Questionnaire [STUQ])
    i. Neurocognition (National Institutes of Health [NIH] Toolbox)
    j. Headache (Headache Impact Test 6 [HIT-6])
7. Assess the indicated biopsychosocial variables as potential moderators of treatment response for PTSD severity:
    a. Comorbid traumatic brain injury (Ohio State University Traumatic Brain Injury Identification Method [OSU TBI] Inventory)
    b. Adverse childhood experiences (Adverse Childhood Experiences Questionnaire [ACE])
    c. Expectancy (Stanford Expectations of Treatment Scale [SETS])
    d. Blast exposure (Blast Exposure Threshold Survey [BETS])
    e. Beliefs about mental health treatment (Endorsed and Anticipated Stigma Inventory- Beliefs About Mental Health Treatment [EASI-BAMHT])
    f. Drug use desire and intent (Drug Use Desire and Intent Questionnaire [DUDIQ])
    g. Treatment readiness (Psychedelic Preparedness Scale [PPS])
    h. Social support (Multidimensional Scale of Perceived Social Support [MSPSS])
    i. Therapeutic alliance (Working Alliance Inventory-Short Revised [WAI-SR])
    j. Life events history (Life Events Checklist [LEC-5])
    k. Alcohol-related problems (Alcohol Use Disorders Identification Test [AUDIT])
    l. Drug-related problems (Drug Abuse Disorders Identification Test [DUDIT])
    m. Psychological flexibility (Multidimensional Psychological Flexibility Inventory-24 [MPFI-24])
    n. Self-compassion (Self-Compassion Scale [SCS])

o. Reaction to touch (Reactions to Touch Measure [RTM])
p. Thwarted belongingness & perceived burdensomeness (Interpersonal Needs Questionnaire [INQ-15])
q. Modified drug effects (Modified Drug Effects Questionnaire [mDEQ-3])
r. Euphoria (Euphoria Assessment Pre-Dosing [EA]-Pre], Euphoria Assessment Post-Dosing [EA-Post])
s. Study blinding (blinding survey)
t. Pharmacogenetic profile (Genomind cheek swab)

8. Characterize between-group changes in fitness for duty by evaluating monthly differences in Medical Profile Status (none, temporary, or permanent) or Limited Duty Status between baseline and follow-up phases.
9. Describe utilization of psychotherapy and psychiatric medications by group between primary and secondary endpoints.
10. Characterize short-term changes in electroencephalography (EEG) signal pre versus during Dosing Session.
11. Characterize short-term changes in EEG signal pre versus 1 day post Dosing Session.
12. Characterize changes in EEG signal observed 1 day post dosing session versus 1 day prior to the next dosing session.

1.3.6 Endpoints

1. The primary endpoint will be 14±3 weeks after the baseline independent rater CAPS-5-R visit and 1-9 days after the final Integration Session.
2. The secondary endpoint will be 13±2 weeks after the third Dosing Session.

1.3.7 Overall Design

The study design is a randomized, double-blind, active-controlled, clinical trial to evaluate MDMA-AT for Active Duty, Guard, and Reserve SMs with PTSD delivered in an MHS setting. Five participants will receive open-label, full-dose MDMA-AT to establish the therapists' adherence to study protocols. A total of 86 participants will then be randomized to either full-dose MDMA-AT or control with low-dose MDMA-AT (see Table 1 and Table 2 for dosing regimens of full-dose and low-dose MDMA-AT, respectively). Participants will be recruited locally from MHS clinics in the National Capital Region and non-locally throughout the MHS. Notable inclusions are an active diagnosis of moderate to severe PTSD (PCL-5 ≥ 38) and command concurrence that the SM is not anticipated to be deployed again in the next two years. Notable exclusions include uncontrolled hypertension, elevated QTc > 450 ms, psychotic spectrum disorders, borderline personality disorder, and any lifetime history of using MDMA.

Each participant will undergo three dosing sessions each approximately one month apart. Dosing sessions may occur in multiple rooms simultaneously with one therapist in each room with the participant, a lead clinician monitoring all rooms via a live audio-video feed, and one additional study team member for each room dedicated to monitoring that room via the live audio-video feed. Up to five participants will be dosed simultaneously across five rooms. The first dosing session is preceded by three 90-minute preparatory sessions over one month, and each of the three dosing sessions is followed by three 90-minute integration therapy sessions over one month. Endpoint measures will occur at one month (primary endpoint) and three months (secondary endpoint) after the last of three dosing sessions.

1.3.7.1 Number of Participants and Study Duration

Five participants will receive full-dose MDMA-AT to establish therapists' adherence to study protocols in an open-label, lead-in training cohort. The randomized cohort will include 86 participants randomized to either full-dose MDMA-AT or the same therapy augmented with low-dose MDMA as active control. Each participant will be engaged with the study for an approximately one-month pre-enrollment screening phase, one-month post-enrollment preparation phase, three-month intervention phase, and two-month follow-up phase. Altogether, the total duration of study engagement for a participant will be approximately 7-8 months (see Figure 1 Study Schema Design).

1.3.7.2 Dose Selection

Table 1. Dosing Regimen of Full-Dose MDMA HCl in Intervention Arm

Dosing Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	120 mg	60 mg	120 mg to 180 mg
3	80 mg (or 120 mg)**	40 mg (or 60 mg)**	80 mg to 180 mg
Total Cumulative Dose			280 mg to 480 mg

*Unless tolerability issues emerge with the initial dose, the participant declines, or vital sign stopping criteria are met for blood pressure (Section 9.7.1), heart rate (Section 9.7.3), or temperature (Section 9.7.5). Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications

**Dose of 3rd Dosing Session will either be the same as the 1st or 2nd Dosing Session and will be based on collaborative shared decision-making between participant and study team. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications

Table 2. Dosing Regimen of Low-Dose MDMA HCl in Control Arm

Dosing Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	40 mg	0 mg	40 mg
2	40 mg	0 mg	40 mg
3	40 mg	0 mg	40 mg
Total Cumulative Dose			120 mg

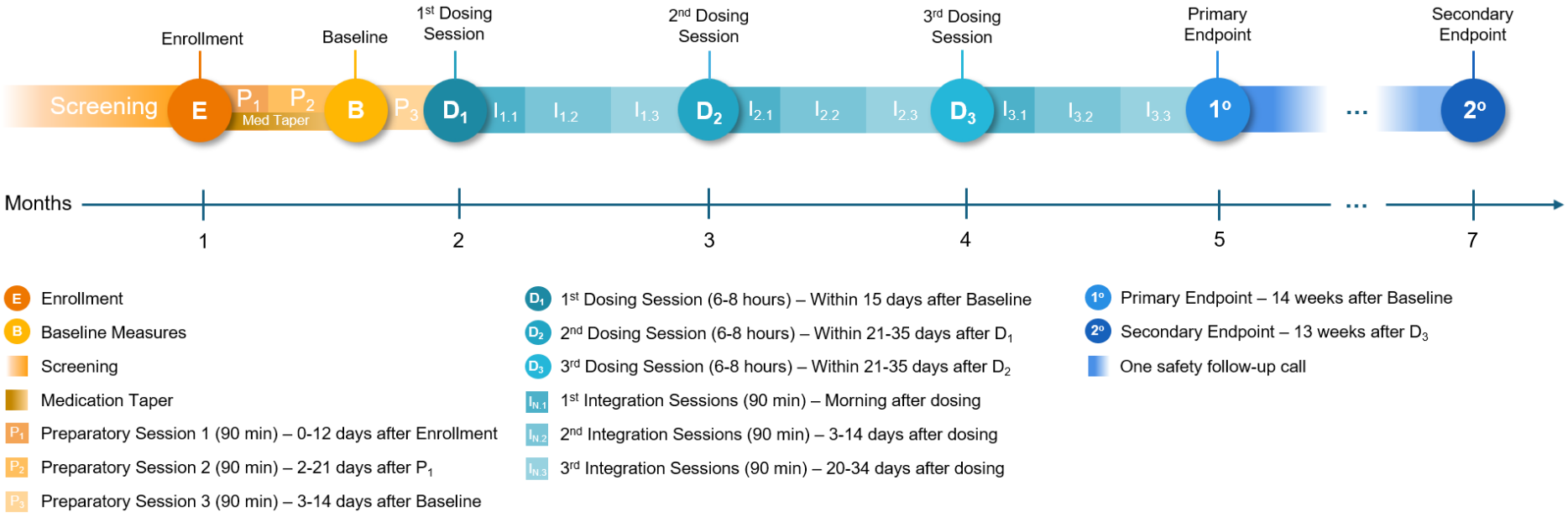
*Unless tolerability issues emerge with the initial dose or the participant declines. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications

1.3.7.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be used in this study to ensure the integrity of data collection and participant safety. See Section 11.5.2 Independent Data and Safety Monitoring Board for more details of the DSMB.

1.4 Study Schema

Figure 1. Study Schema Diagram



1.5 Timelines of Study Activities and Measures

Table 3. Timeline of Screening and Preparation Phases

Phase	**Screening Phase**					**Preparation Phase**				
Visit	**S_1**	**S_2**	**S_3**	**S_4**	**EN**	**P_1**	**P_2**	**MT**	**B_1**	**P_3**
Visit Number	**-**	**-**	**-**	**-**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**
Visit Description	Prescreening Questionnaire & Phone Call	Informed Consent	Clinician-Administered Screening	Medical Screening	Enrollment	1st Preparation Session	2nd Preparation Session	Medication Taper Phone Call	Baseline CAPS-5-R Independent Rater and Baseline Measures[a]	3rd Preparation Session
Visit Timing	Before S_2	Day 0	1-28 days after S_2; Before EN	1-28 days after S_2; Before EN	1-14 days after S_3 and S_4 complete	0-12 days after EN	2-21 days after P_1	0-7 days after taper ends; ≤56 days after EN; Before P_3	0-14 days after MT[a]	3-14 days after B_1 completed; 1-4 days (ideally 1 day) before D_1
Visit Type	Asynchronous & Phone	Virtual or F2F	Virtual or F2F	Asynchronous	Virtual or F2F	Virtual or F2F	Virtual or F2F	Phone	Virtual or F2F	F2F (or virtual)
Study Activities										
Study Informed Consent	X_{Give}	$X_{Completed}$								
HIPAA Authorization Form	X_{Give}	$X_{Completed}$								
Command Approval Form	X_{Give}			$X_{Completed}$						
Pre/Post-Dosing Instructions	X_{Give}	X_{Review}				X_{Review}	X_{Review}			X_{Review}
Medication Taper		X[b]		X[c]	X[d]	X	X	X		
Measures (see Table 6)	X[e]		X[e]	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]
Adverse Event Collection						X	X	X		X
Medication Reconciliation				X		X	X	X		X
Physical Exam				X		X[f]	X[f]			X[f]
Vitals, Height, & Weight				X						
Medical/Psychiatric History				X						
EKG, 12-lead				X						
Eligibility Check	X		X	X	X			X	X	X
90-minute Therapy Session						X	X			X
EEG Headphones										X
Labs										
bHCG Screen, Urine				X						
Drug Screen, Urine				X						
BMP & Liver Panel				X						X
CBC, TSH, T3/T4 (if needed)				X						
Pharmacogenomics Swab										X

Abbreviations: B_1, baseline session 1; bHCG, beta human chorionic gonadotropin; BMP, basic metabolic panel; CBC, complete blood count; EEG, electroencephalography; EN, enrollment; EKG, electrocardiogram; F2F, face-to-face; HIPAA, Health Insurance Portability and Accountability Act; MT, medication taper phone call; P_n, preparatory session #n; POC, point-of-care; S_n, screening session #n; TSH, thyroid-stimulating hormone.

Note for Table 3: [a], the baseline measures that are not the CAPS-5-R may be completed across 1-3 sessions within a 7-day period; [b], study staff will recommend that a participant make an appointment with their prescriber(s) to develop a medication taper plan; [c], study physician discusses the risks and benefits of medication taper initiation +-with the patient and their prescriber(s); [d], initiate medication taper, study therapists will check in with participants once weekly during their medication tapering period via phone to administer the C-SSRS, check for AEs, and concomitant meds, with preparation sessions counting as one of those check-ins; [e], see Table 6 for list of measures; [f], physical exam conducted only once by qualified study staff any time between enrollment and P_3; x_{Give}, document given to the participant; $x_{Completed}$, completed document returned to study staff; x_{Review}, document reviewed.

Table 4. Timeline of Intervention and Follow-Up Phases

Phase	Intervention Phase													Follow-up Phase		
	Cycle 1					Cycle 2				Cycle 3						
Visit	**R**	**D_1**	**$I_{1.1}$**	**$I_{1.2}$**	**$I_{1.3}$**	**D_2**	**$I_{2.1}$**	**$I_{2.2}$**	**$I_{2.3}$**	**D_3**	**$I_{3.1}$**	**$I_{3.2}$**	**$I_{3.3}$**	**1°**	**F**	**2°**
Visit Number	-	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**
Visit Description	Random-ization	1st Dosing	Integra-tion	Integra-tion	Integra-tion	2nd Dosing	Integra-tion	Integra-tion	Integra-tion	3rd Dosing	Integra-tion	Integra-tion	Integra-tion	Primary Endpoint	Follow-up Safety Call	Second-ary Endpoint
Visit Timing	Within 14 days of B_1; After P_3; 12-48h before D_1	Within 15 days of B_1	Morning after D_1	3-14 days after D_1	20-34 days after D_1; 1-7 days before D_2	21-35 days after D_1	Morning after D_2	3-14 days after D_2	20-34 days after D_2; 1-7 days before D_3	21-35 days after D_2	Morning after D_3	3-14 days after D_3	20-35 days after D_3	1-9 days after $I_{3.3}$; 14±3 weeks after B_1	4±1 weeks after 1°	13±2 weeks after D_3
Visit Type	Asynch ronous	F2F	F2F	F2F or Virtual	F2F	F2F	F2F	F2F or Virtual	F2F	F2F	F2F	F2F or Virtual	F2F or Virtual	F2F or Virtual	Phone	F2F or Virtual
Study Activities																
Randomization	x															
Measures (See Table 6)		x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]	x[d]
AE, AESI, SAE Collection		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication Reconciliation		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EEG Headphones		x	x		x	x	x		x	x	x					
Vital Signs & Holter EKG		x				x				x						
90-min Therapy Session			x	x	x		x	x	x		x	x	x			
Pre/Post-Dosing Instructions				x_{Review}	x_{Review}			x_{Review}	x_{Review}							
Phone Check-ins			x[e]	x[e]			x[e]	x[e]			x[e]	x[e]				
Labs																
Alcohol Breathalyzer		x				x				x						
POC Drug Screen, Urine		x				x				x						
POC bHCG Screen, Urine		x				x				x						
bHCG Screen, Urine												x[f]				
Liver Panel & BMP			x		x		x		x		x					

Abbreviations: 1°, primary endpoint; 2°, secondary endpoint; AE, adverse event; AESI, Adverse Event of Special Interest; bHCG, beta human chorionic gonadotropin; BMP, basic metabolic panel; CBC, complete blood count; D_n, dosing Session #n; EEG, electroencephalography; EKG, electrocardiogram; F2F, face-to-face; I_n, integration session #n; F, follow-up phone call between primary and secondary endpoint; min, minute; POC, point-of-care; R, randomization; SAE, Serious Adverse Event; TSH, thyroid-stimulating hormone. Note for Table 4: [d], see Table 6 for list of measures; [e], brief phone check-ins conducted between each 1st and 2nd Integration Sessions ($I_{n.1}$ and $I_{n.2}$), between each 2nd and 3rd Integration Sessions ($I_{n.2}$ and $I_{n.3}$), and on as-needed basis; [f], participants will be informed to obtain a final urine pregnancy test from the lab between 3 days after their final dosing and primary endpoint; x_{Review}, session-relevant items from document reviewed.

Table 5. Timeline of Study Measures

Phase	Time (min)	Screening Phase			Preparation Phase					Intervention Phase												Follow-up Phase		
										Cycle 1				Cycle 2				Cycle 3						
Visit Code		S_1	S_3	EN	P_1	P_2	MT	B_1	P_3	D_1	$I_{1.1}$	$I_{1.2}$	$I_{1.3}$	D_2	$I_{2.1}$	$I_{2.2}$	$I_{2.3}$	D_3	$I_{3.1}$	$I_{3.2}$	$I_{3.3}$	1°	F_1	2°
Visit Number		-	-	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21
CAPS-5-R (Primary)	90							x														x		x
LEC-5	2	x							x				x				x					x		x
PCL-5 (after LEC-5)	5-10	x							x				x				x					x		x
SCID-5-SPQ	20		x																					
SCID-5-PD	15		x[h]																					
MINI	15-20		x																					
OSU-TBI	3-5		x																					
C-SSRS (Lifetime)	5		x																					
C-SSRS (Last month)	5		x		x																			
C-SSRS (Since Last Visit)	5					x	x	x	x	x[g]	x	x	x	x[g]	x	x	x	x[g]	x	x	x	x	x	x
MPSQ	3		x		x				x				x				x					x	x	x
DUDIQ	0-1				x	x			x		x	x	x		x	x	x		x	x	x	x	x	x
PPS-Prospective	4				x	x			x			x	x			x	x							
PPS-Retrospective	4										x				x				x					
BDI-II	5-10							x														x		x
PSQI	5-10							x														x		x
PEG	1							x					x				x					x		x
EASI (BAMHT Scale)	1-2							x														x		x
BETS	15							x																
HIT-6	5							x					x				x					x		x
NIH Toolbox	25							x														x		x
MIOS	2-4							x					x				x					x		x
MPFI-24	5							x					x				x					x		x
SCS-SF	2							x														x		x
RTM	5																		x					
ACE	3-5							x																
MSPSS	2							x														x		x
INQ-15	3							x														x		x
PIES	5							x														x		x
HPQSF	3-5							x														x		x
WHOQOL-BREF	5-10							x														x		x
WHODAS 2.0	5-20							x														x		x
SETS	2							x																
AUDIT	2-3							x																
DUDIT	2-3							x																
TLFB (Alcohol)	5-10							x					x				x					x		x
STUQ	1-2							x					x				x					x		x

Phase	Time (min)	Screening Phase			Preparation Phase					Intervention Phase												Follow-up Phase		
										Cycle 1				Cycle 2				Cycle 3						
Visit Code		**S_1**	**S_3**	**EN**	**P_1**	**P_2**	**MT**	**B_1**	**P_3**	**D_1**	**$I_{1.1}$**	**$I_{1.2}$**	**$I_{1.3}$**	**D_2**	**$I_{2.1}$**	**$I_{2.2}$**	**$I_{2.3}$**	**D_3**	**$I_{3.1}$**	**$I_{3.2}$**	**$I_{3.3}$**	**1°**	**F_1**	**2°**
Visit Number		**-**	**-**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**
DUQ (Baseline)	5							x														x		
DUQ (Follow-Up)	1-3												x				x					x		
DUQ (Longterm Follow-Up)	1-3																							x
WAI-SR	3-5								x				x				x				x			
CAM	5									x[g]				x[g]				x[g]						
EA-Pre	0-1									x				x				x						
EA-Post	0-1									x				x				x						
mDEQ-3	0-1										x				x				x					
Blinding Survey	1-2										x				x				x					x
TFA	3																					x		
Qualitative Interview	45-60																					x		
Total Time (min)	-	7-12	63-70	3	9-10	9-10	5	204-249	22-30	10-12	10-13	9-10	42-60	10-12	10-13	9-10	42-60	10-12	15-18	5-6	8-11	239-303[i]	8-9	187-237[i]

Abbreviations: 1°, primary endpoint; 2°, secondary endpoint; ACE, Adverse Childhood Experiences Questionnaire; AUDIT, Alcohol Use Disorders Identification Test; B_n, baseline session #n; BDI-II, Beck Depression Inventory-II; BETS, Blast Exposure Threshold Survey; CAPS-5-R, Clinician-Administered PTSD Scale for DSM-5 Revised; CAM, Confusion Assessment Method; C-SSRS, Columbia-Suicide Severity Rating Scale; D_n, dosing session #n; DUDIQ, Drug Use Desire and Intent Questionnaire; DUDIT, Drug Abuse Disorders Identification Test; DUQ, Drug Use Questionnaire; EA-Post, Euphoria Assessment Post-Dosing; EA-Pre, Euphoria Assessment Pre-Dosing; EASI (BAMHT Scale), Endorsed and Anticipated Stigma Inventory; EN, enrollment; F_1, follow-up safety phone call; HIT-6, Headache Impact Test 6; HPQSF, Health and Work Performance Absenteeism and Presenteeism Short Form; I_n, integration session #n; INQ-15, Interpersonal Needs Questionnaire; LEC-5, Life Events Checklist; mDEQ-3, Modified Drug Effects Questionnaire; min, minute; MINI, Mini International Neuropsychiatric Interview; MIOS, Moral Injury Outcome Scale; MPFI-24, Multidimensional Psychological Flexibility Inventory-24; MPSQ, Medical Profile Status Questionnaire; MSPSS, Multidimensional Scale of Perceived Social Support; MT, medication taper phone call; NIH, National Institutes of Health; OSU-TBI, Ohio State University Traumatic Brain Injury Identification Method; P_n, preparatory session #n; PCL-5, PTSD Checklist for DSM-5; PEG, Pain, Enjoyment of Life and General Activity Scale; PIES, Perceived Invalidation of Emotion Scale; PPS, Psychedelic Preparedness Scale; PSQI, Pittsburgh Sleep Quality Index; R, randomization; RTM, Reactions to Touch Measure; S_n, screening session #n; SCID-5-PD, Structured Clinical Interview for DSM-5 Personality Disorders; SCID-5-SPQ, SCID-5 Self-report Personality Questionnaire; SETS, Stanford Expectations of Treatment Scale; SCS-SF, Self-Compassion Scale Short Form; STUQ, Smoking and Tobacco Use Questionnaire; TFA, Theoretical Framework of Acceptability; TLFB, Timeline Follow-Back Calendar, Alcohol; WAI-SR, Working Alliance Inventory-Short Revised; WHOQOL-BREF, World Health Organization Quality of Life – Brief Version; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0.

Note for Table 5: [g], Administered twice on Dosing Session days – 1st pre-dosing and 2nd at end of Dosing Session; [h], SCID-5-PD only administered if SCID-5-SPQ screens positive for a personality disorder; [i], may be over 1-3 sessions across a 7-day period.

2 Introduction

MDMA (±3,4-methylenedioxymethamphetamine or midomafetamine), otherwise known in recreational settings as "Ecstasy" or "Molly," is primarily being studied as an augmenting agent to psychotherapy for PTSD. Eight randomized clinical trials that included a total of 171 participants randomized to receive MDMA at starting doses of 75 mg to 125 mg (with a supplemental half-dose 90-120 minutes later) in comparison to 126 participants randomized to receive an inactive placebo or up to 40 mg of MDMA found that MDMA-AT was an efficacious treatment for PTSD with moderate to large between-group effect sizes (Cohen's d = 0.70-0.91) and large within-group effect sizes (Cohen's d = 1.4-2.10).[1,3,4]

The FDA designated MDMA-AT as a Breakthrough Therapy in 2017, which is reserved for treatments that may represent substantial improvement over current treatment options.[6] FDA-approved Expanded Access (colloquially known as "Compassionate Use") began in 2022, authorizing access to open-label MDMA-AT within FDA-regulated *treatment* settings outside of clinical trials. The first two Phase 3 trials of MDMA-AT for PTSD completed in 2023, and the New Drug Application was submitted to the FDA in December 2023. On 9 August 2024, the FDA declined to approve the New Drug Application due in part to several limitations in study design of the Phase 3 trials. However, the FDA recommended one more Phase 3 trial that addresses the limitations of previous clinical trials, at which point the FDA will accept a resubmission of a New Drug Application. Although our study will not be the Phase 3 trial that the FDA is requesting, our study systematically addresses the study design limitations of previous studies while also aiming to inform the potential clinical implementation of MDMA-AT in a MHS setting for military SMs with PTSD.

2.1 Study Rationale

PTSD is a debilitating psychiatric condition that affects a disproportionate number of Active Duty (AD) SMs and Veterans.[1,7] MDMA produces a profile of subjective effects that appear to enhance psychotherapy by reducing defenses, increasing distress tolerance, and fostering empathy.[1] MDMA-AT has been successfully studied in combination with psychotherapy to improve clinical and functional outcomes in those with PTSD. MDMA-AT may be FDA-approved in the near future, yet it has not been studied in AD SMs.[8] This randomized, double-blind, active-controlled clinical trial aims to determine the safety, efficacy, durability, acceptability, and tolerability of MDMA-AT delivered in an MHS setting for SMs with PTSD.

MDMA-Assisted Therapy for PTSD. Six phase 2 studies[1] and two phase 3 multi-centered studies[3,4] – all in civilians, one fourth of whom are veterans – show moderate to large effect sizes (Cohen's *d* = 0.7-0.91, between-group; *d* = 1.4-2.1, within-group) with 67-71% no longer diagnosable with PTSD,[3,4] compared to 28-40% after Prolonged Exposure (PE) or Cognitive Processing Therapy (CPT).[2] Dropout rates are lower for MDMA-AT (4%)[3,4] than in PE & CPT (27-56%).[9] Rates of PTSD remission after MDMA-AT significantly continue to improve at 1-year follow-up[1] and have sustained durability 3.8 years later.[10]

DoD Political & Regulatory Landscape. Section 723 of the 2024 NDAA authorizes the DoD to study MDMA-AT in AD SMs.[5] Independent of NDAA 2024, DoD regulations detail a clear legal pathway to conduct MDMA-AT clinical trials.[8] The Department of Veterans Affairs (VA) is now also funding studies of MDMA-AT, and clinical trials of MDMA-AT for veterans with

PTSD are currently being conducted in at least seven VA medical centers. Yet, no studies have yet been conducted for AD SMs. Further studies are needed to 1) assess the clinical and operational impacts of MDMA-AT in AD SMs and 2) inform post-FDA-approval implementation of MDMA-AT within the MHS. This study aims to evaluate the clinical and operational impacts of MDMA-AT for SMs with PTSD in an MHS setting.

The Access Problem & Simultaneous Dosing as a Proposed Solution. MDMA-AT will likely be in high demand by SMs in a potential post-FDA approval landscape, and waitlists will likely be long. For example, the waitlist was over 1,400 patients long for the first 50 slots in the first FDA-approved Expanded Access ("Compassionate Use") treatment setting for MDMA-AT. Access to MDMA-AT will be a major challenge, and this challenge is further compounded by the fact that MDMA-AT as implemented by the New Drug Application sponsor is resource-intensive, requiring > 40 hours with 2 therapists (i.e., > 80 therapist-hours) over 3 medication sessions, versus 12-18 hours with current first-line therapies.

This resource-intensiveness compounded with high demand will potentially result in long waitlists that may encourage some SMs to seek these drugs in illicit settings. To avoid the potential negative medical and operational consequences associated with illicit use, it will be imperative to increase access to FDA-approved medical settings that are safe, legal, and resource-efficient.

We anticipate that the primary avenue that may have the greatest impact in improving resource-efficiency and access over the traditional 2-therapist-1-patient model is the Simultaneous Dosing model. In the Simultaneous Dosing model, multiple rooms will be running simultaneously during the MDMA dosing sessions with one therapist in the room instead of two, and there will be an additional room where a supervising clinician will be monitoring live video feeds to each of the rooms. If this model is adopted in clinical practice, five patients may be treated with six clinicians instead of ten. This clinical trial will be studying this model of Simultaneous Dosing.

2.2 Background

2.2.1 PTSD

PTSD is a psychiatric condition characterized by directly or indirectly experiencing a traumatic event that leads to persistent symptoms of hyperarousal (e.g., hypervigilance, exaggerated startle reflex, irritability, etc.), avoidance (of memories or queues), intrusion (e.g., nightmares, flashbacks, etc.), and altered mood and cognition (e.g., excessive guilt or self-blame, social detachment, etc.).[11]

PTSD is prevalent in 10-18% of AD SMs after a deployment,[12,13] in 4-17% of veterans,[14] and in 4-8% of the general population.[15-17] PTSD is the most common psychiatric diagnosis for medical discharge in all branches, and it is the most common diagnosis (medical or psychiatric) for medical discharge from the Army.[18] Nearly 10,000 SMs with PTSD are medically discharged annually,[19] joining the 1.1 million Veterans who receive service-connected disability for PTSD with annual healthcare costs of up to $1.35 billion.[20,21] Approximately half of individuals with PTSD suffer from comorbidities such as depression and insomnia which can worsen PTSD severity and increase the risk of suicidality. Rates of completed suicide are 4-7 times higher in

those with PTSD compared to the general population.[22] Overall, PTSD contributes substantially to morbidity & mortality in both AD SMs and Veterans.

PE and CPT are currently the most well studied, gold-standard, first-line treatments for PTSD.[23] Despite this, they are less efficacious for military-related PTSD compared to non-military-PTSD.[19] Of individuals with military-related PTSD who receive PE and CPT, approximately one third (28-40%) of individuals no longer meet diagnostic criteria for PTSD, 12-20% of individuals achieve remission, and 13-56% drop out of treatment.[20,21] Furthermore, antidepressants must be taken daily to sustain potential symptomatic benefits and avoid withdrawal symptoms. Whereas, the treatment protocol proposed for this study requires administering MDMA only three times in total.

Currently available medications are less efficacious than trauma-focused psychotherapies for PTSD.[24] The antidepressants sertraline and paroxetine are the only two medications approved by the FDA to treat PTSD. Yet, their low to moderate efficacy when used alone[25] has led them to be considered second-line treatments for PTSD.[23] Their efficacy for PTSD further diminishes to being indistinguishable from placebo when combined with trauma-focused psychotherapy.[17,26] Augmenting psychotherapy with several other FDA-approved medications used off-label for PTSD has revealed some positive findings,[27] though none thus far have been reliably superior over placebo.[28] MDMA-AT was the only medication-assisted therapy to have a statistically significant effect for the treatment of PTSD.[28]

2.2.2 MDMA

2.2.2.1 History

MDMA was first synthesized in 1912 by Anton Köllisch, a chemist working for the pharmaceutical company, Merck, as a precursor to a hemostatic agent.[29] However, its psychoactive properties remained unrecognized for several decades. The first known synthesis of MDMA to study its potential for clinical use was a 1953 study contracted by the U.S. Army Chemical Corps and conducted by the University of Michigan.[30] This was an animal toxicology study to estimate safe doses of MDMA and several other similar substances such as 3,4-methylenedioxyamphetamine (MDA), a metabolite of MDMA.[31] While MDA would later be used in government-funded research, there is no record of MDMA being studied or administered to humans in a government-supported project.[32]

MDA, an entactogen similar to MDMA, was patented in 1960 to treat anxiety and was used throughout the 1960-70s both recreationally and as an adjunct to psychotherapy, similar to how MDMA-AT is conducted today.[30,33] Once MDA was made a Schedule I substance by the passage of the 1970 Controlled Substances Act, MDMA first surfaced that same year on the streets of Chicago as an unscheduled recreational alternative to MDA.[30] Alexander Shulgin, a pioneer of the chemistry of psychedelic and entactogenic compounds, also facilitated the synthesis of MDMA during this period and began self-trials with MDMA in 1976.[30] In 1977, Shulgin introduced it to retired Army Lieutenant Colonel Leo Zeff, an Oakland, California psychotherapist with years of experience in MDA-assisted therapy throughout the 1960s. Zeff went on to train approximately 150 therapists and legally treat over 4,000 patients with MDMA-AT until 1985, when MDMA was declared a Schedule I substance with no accepted medical use due to the rise of its use in recreational settings.[29]

The first report of the clinical use of MDMA was also published in 1985 and it involved a summary of proceedings from a gathering of 35 clinicians and researchers experienced in the use of MDMA.[34] The report described that MDMA "reduced defensiveness and fear of emotional injury, thereby facilitating more direct expression of feelings and opinions, and enabling people to receive both praise and criticism with more acceptance than usual… Many subjects experienced the classic retrieval of lost traumatic memories, followed by the relief of emotional symptoms.[34]"

Given that by 1985 MDMA had been used for therapeutic purposes to treat various psychiatric conditions for over a decade, court proceedings were initiated to determine if there was a more appropriate scheduling for MDMA than a Schedule I substance with "no accepted medical use." Supporting data included clinical findings of safety and efficacy presented by MDMA-AT therapists.[35] The DEA administrative law judge presiding over the case ultimately determined that "the evidence of record requires MDMA to be placed in Schedule III[36]" – meaning that MDMA has an accepted medical use and low to moderate risk of physical dependence or high psychological dependence.[37] Despite this ruling, the DEA determined in 1986 that MDMA should remain Schedule I with no accepted medical use for reasons that remain unclear.

The Multidisciplinary Association for Psychedelic Studies (MAPS), a non-profit organization, was subsequently founded in 1986 in response to the DEA Schedule I determination. The primary effort of MAPS has been building an evidence base towards FDA-approval of MDMA-AT for PTSD. All the published randomized placebo-controlled Phase 2 and 3 studies conducted of MDMA-AT for PTSD have thus far been sponsored by MAPS. The MAPS Public Benefit Corporation, which was their drug development entity, was rebranded as Lykos Therapeutics prior to their submission of the New Drug Application in early 2024 and rebranded again to Resilient Pharmaceuticals in 2025.

2.2.2.2 Pharmacology and Neuroscience

MDMA is a triple monoamine reuptake inhibitor that is predominantly serotonergic by blocking serotonin, norepinephrine, and dopamine reuptake in descending order of affinity and degree of elevation of extracellular transmitter levels.[38,39]

Oxytocin appears to also be an important mediator underlying some of MDMA's effects.[40] For several hours after MDMA administration, plasma oxytocin reaches levels up to four times greater than baseline,[41] an effect that is unique to MDMA and not observed with lysergic acid diethylamide (LSD) or D-amphetamine.[20] In a rodent model, MDMA induces oxytocin release via 5-HT activation of presynaptic 5-HT_4 receptors on oxytocin neurons, and subsequent activation of oxytocin receptors in the nucleus accumbens reopens the age-related closure of a critical period of neuroplasticity that temporarily enhances social reward learning.[40] This oxytocinergic effect may underlie feelings of greater trust,[42] openness to social reward and connectedness,[42] and modulate encoding of stimuli as aversive versus neutral.[43]

Reductions in the fear response with MDMA are supported by decreased activity in the amygdala in response to socially threatening stimuli during MDMA administration.[44] When MDMA is administered to rodents during reconsolidation of an extinguished cue-shock association, the learning of the new safety memory is strengthened.[45] Likewise, in humans, MDMA administered after threat conditioning and prior to extinction training results in a greater

proportion of individuals demonstrating extinction retention 2 days later relative to inactive placebo.[46]

2.2.2.3 Objective Effects

MDMA elicits acute sympathomimetic effects including elevated blood pressure, heart rate, body temperature, and pupillary dilation.[4,20,47,48] MDMA at doses of 75-125 mg in healthy participants elicits temporary hypertension (33% of participants), tachycardia (29%), and increased body temperature >38°C (19%) which is typically a relative increase of approximately 1 degree.[47] MDMA exhibits dose-dependent effects, such that higher doses and plasma blood concentrations are associated with greater elevations in hemodynamic response.[47,48] Because MDMA is primarily metabolized by CYP2D6, CYP2D6 activity is inversely related to MDMA plasma concentrations,[48] subjective drug effects,[49] and blood pressure[49] after MDMA administration. Given this finding, our clinical trial will collect pharmacogenomic profiles to explore whether CYP2D6 metabolism potentially moderates treatment effect.

A randomized, double-blind, cross-over study comparing MDMA (125 mg), LSD (100 μg), D-amphetamine (40 mg), and inactive placebo in healthy participants found that the three active drugs had comparable increases in hemodynamic response, body temperature, and pupillary dilation.[20] Compared to D-amphetamine, however, MDMA and LSD had comparably greater increases in heart rate and lesser increases in blood pressure.[20] Overall, MDMA produces a constellation of sympathomimetic effects that are well-tolerated but must still be monitored in clinical contexts.

2.2.2.4 Subjective Effects

"Classical psychedelics" like LSD and psilocybin are known to cause vivid visual perceptual phenomena,[50] mystical or spiritual experiences,[51] a dissolution of the ego or sense of self,[52] and a sense of unity or interconnectedness with all else.[53] Whereas, MDMA at therapeutic doses does *not* markedly produce the aforementioned subjective effects that are characteristic of classical psychedelics.[20] Although MDMA at therapeutic doses is potentially associated with mild transient depersonalization or derealization phenomena, it does not produce visual perceptual phenomena or panic reactions which are more strongly associated with classical psychedelics.[54] MDMA instead produces a state of positive mood, well-being, and extroversion that is not attenuated by the serotonin $(5HT)_{2A/C}$ antagonist ketanserin.[55] Therefore, MDMA is not considered a classical psychedelic because $5HT_{2A}$ agonism is the primary mechanism of action characteristic of classical psychedelics,[56] and the subjective effects of MDMA are not attenuated by a $5HT_{2A}$ antagonist.[55]

The first academic publication of the clinical effects of MDMA was the 1985 proceedings from a meeting of 35 experts that included experienced researchers and clinicians.[34] The report included a comparison of the subjective effects of MDMA and LSD that noted "[u]nlike LSD, MDMA does not essentially cause perceptual or cognitive distortions or loss of ego control. MDMA consistently promotes a positive mood state, while LSD promotes mood swings that can be extreme and unpredictable. MDMA's principal effects last 3 to 5 hours, whereas those of LSD last 6 to 14 hours. The clinicians agreed that MDMA was much easier to use than LSD, and because MDMA did not threaten ego control, it involved little psychological risk to a naïve subject. While LSD subjects sometimes experience transient delusional states, the only

complications of using MDMA, according to the clinicians and researchers, are occasional anxiety and various physical symptoms due to the drug's sympathomimetic effects."[34]

More rigorous modern studies have corroborated many of the claims in the initial 1985 report. Notably, a randomized, double-blind, cross-over study of 28 healthy participants who received LSD (100 μg), MDMA (125 mg), D-amphetamine (40 mg), and inactive placebo at least 10 days apart found that the subjective effects of MDMA are more comparable to D-amphetamine than to LSD.[20] Unlike with LSD, perceptual and cognitive lucidity remain intact with both D-amphetamine and MDMA.[20] The primary differences that separate MDMA from other commonly prescribed amphetamines are the additional subjective effects of bliss and self-compassion, as well as pro-social effects including heightened empathy, trust, compassion, and sense of connectedness to others.[20,57] Notably, a study comparing separate clinical trials of MDMA and methamphetamine in healthy subjects suggests MDMA and methamphetamine may have comparable effects on prosocial perceptions of social connection.[58] Furthermore, MDMA has been found to increase feelings of self-reported sociability,[44] to enhance implicit and explicit emotional empathy for positive emotional stimuli more so in men than women,[59,60] to reduce rejection of unfair offers in a partnered economic decision-making game,[61] and to enhance attention to positive social cues and pleasantness of experienced affective touch.[62]

Thus, MDMA is best classified as a non-classical psychedelic and more specifically, an *empathogen* or *entactogen*. Empathogen refers to a core characteristic of MDMA to "generate empathy." Entactogen is the more widely accepted term referring to the way in which MDMA allows an individual to "touch within" through a lens of inner-directed self-compassion.[63] MDMA's entactogenic characteristics are thought to be central to its therapeutic effects when paired with psychotherapy.[64]

When discussing safety profiles, a clear distinction must be made between recreational "Ecstasy" used in non-clinical settings versus pharmaceutical-grade MDMA used in controlled clinical settings. MDMA itself is considered to have a low risk of dependence and harm relative to many other prescribed and non-prescribed substances.[65,66] However, the risks are greater with Ecstasy, which often does not contain pure MDMA and is typically taken in uncontrolled, non-clinical environments. Approximately half of Ecstasy pills contain adulterants such as cocaine, amphetamines, or fentanyl, and some pills may not contain MDMA at all.[67,68] Many cases of toxicity in the literature attributed to MDMA are in fact not confirmed by laboratory testing to be MDMA, but rather, they depend on patient or collateral report of Ecstasy use, which is often confounded by other substances.[69-71] Thus, conclusions drawn from studies of Ecstasy used in non-clinical settings cannot be directly translated to pharmaceutical-grade MDMA administered in a controlled clinical setting. The potential risks associated with the use of MDMA and their mitigation strategies are thoroughly detailed and discussed in Section 2.3 Risk Assessment.

2.2.3 MDMA-Assisted Therapy for PTSD

2.2.3.1 Overview

Nearly 300 study participants have received MDMA-AT for PTSD across eight randomized placebo-controlled clinical trials.[3,4,72-77] Participants had a diagnosis of PTSD for 14-18 years on average, and nearly all were resistant to previous therapies.[1,3,4]

At the primary study endpoint (approximately 4 weeks after the last of 3 MDMA doses) across both Phase 3 multi-center clinical trials, 67-71% of individuals no longer met diagnostic criteria for PTSD after a course of MDMA-AT versus 32-48% with placebo-assisted therapy (Cohen's d = 0.70-0.91 between-group, d = 1.95-2.1 within-group).[3,4] In Phase 2 studies, rates of no longer meeting PTSD diagnostic criteria significantly further improved at 1-year follow-up[1] and remain durable, with 74% no longer meeting diagnostic criteria for PTSD nearly four years later.[10]

Full remission (defined as loss of PTSD diagnosis and Clinician Administered PTSD Scale for DSM-5 total score < 11) was achieved by 33% of the active group and 5% of the placebo group in the first Phase 3 trial[4] as well as 46% of the active group and 21% of the placebo group in the second Phase 3 trial.[3] Dropout rates across both Phase 3 trials over the 3-4 month treatment course were 5% with MDMA-AT and 17% in the placebo group.[1,3,4] This compares to PE and CPT with 12-20% full remission and 47-56% dropout.[9]

2.2.3.2 Mechanisms

Many therapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in therapy with an appropriate level of emotional engagement. To be effective, exposure must be accompanied by a degree of emotional engagement or "fear activation" while avoiding dissociation or overwhelming emotion. This has been referred to as working within the "optimal arousal zone" or "window of tolerance."[78] MDMA-AT appears to substantially widen this window of tolerance, thus allowing the individual to process traumatic experiences without disengaging or avoiding in a manner they otherwise might without MDMA.[1] What may contribute to this widening of the window of tolerance is the way in which MDMA enhances interpersonal trust,[42] self-compassion,[79] openness to social reward and connectedness,[42] and encoding of otherwise aversive stimuli as neutral[43] – all of which allow the individual to better tolerate trauma-processing without disengagement or avoidance in a therapeutic context.

PTSD is associated with elevated amygdala activity and decoupling of amygdala functional connectivity from cortical regions associated with emotional control.[80-82] This decoupling is associated with heightened amygdala reactivity to threatening queues and impaired emotional regulation. fMRI studies have demonstrated MDMA in those with symptoms of PTSD led to improvement in functional connectivity between the amygdala and cortical regions associated with emotional regulation, suggesting enhanced top-down regulatory control of cortical regions over limbic structures involved in fear and trauma memory processing.[83,84] Furthermore, the degree of improvement in cortico-limbic connectivity was significantly associated with the degree of improvement in PTSD symptoms per the CAPS-IV.[83] Altogether, the subjective and neurobiological effects of MDMA facilitate a psychological state that is productive to trauma-processing in a therapeutic context.

2.2.3.3 Modality

MDMA-AT primarily consists of three distinct types of sessions: preparatory, dosing, and integration sessions. A treatment course involves 3 dosing sessions. Each dosing session is 6-8 hours long and is approximately one month (± 1 week) apart. Preceding the first MDMA session are three 90-minute preparatory sessions designed to educate the participant about the treatment, build a therapeutic alliance, and establish therapeutic aims.

Each MDMA session is followed by three 90-minute integration sessions for a total of 6-9 integration sessions per course of treatment. The first of each trio of integration sessions occurs the morning after the MDMA session. The 2nd and 3rd integration sessions follow at approximately one-week intervals but prior to the next MDMA session.

Each MDMA session involves two doses of MDMA. Similar to previous Phase 3 trials, the first dose of each full-dose MDMA session in our trial ranges from 80-120 mg. The second supplemental dose is half of the initial dose and is offered 2 hours (± 15 minutes) after the initial dose as an option based on tolerability, patient preference, and therapist clinical judgment. In MDMA-AT clinical trials, participants were offered and had accepted the supplemental dose in nearly all cases. The purpose of the timing and dosage of the supplemental dose is to extend the peak effects of the MDMA.

The therapeutic modality of MDMA-AT is derived fundamentally from elements of a person-centered, process-oriented approach that endeavors to establish a dynamic of trust, respect, and supportive self-discovery while providing non-directive support. As long as these elements are prioritized, the Treatment Manual used in the Phase 2 and 3 trials entrusts the therapeutic framework for the content and technique of therapeutic engagement to be guided by the therapist's prior psychotherapeutic training. However, our study differs from this approach in that the therapeutic framework will be guided by principles of Acceptance and Commitment Therapy as the central therapeutic framework.[85] The therapeutic framework is described in further detail in the study Treatment Manual which study clinicians will be trained on prior to the study.

2.3 Risk Assessment

Clinical trials of MDMA-AT inherently feature several potential risks that can be categorized into medical, psychiatric, and relational domains. Medical risks include the potential development or exacerbation of hyponatremia, hyperthermia, neurocognitive conditions, cardiac and cardiovascular conditions, and other medical comorbidities. Psychiatric risks include the potential development or exacerbation of psychiatric symptoms such as suicidality, depression, anxiety, psychosis, addiction, and other psychiatric comorbidities. A final domain of risks is inherent in the relationship between the participant and the therapist, to include the potential for sexual abuse, suggestibility, and interpersonal dependency.

The design of our study not only meticulously accounts for each of these risks but also implements layers of safeguards throughout recruitment, screening, enrollment, and preparation/dosing/integration sessions in the form of thorough medical screening and monitoring, extensive training of study team members, and various elements inherent in the study design and conduct to maximize participants' safety.[86]

2.3.1 Mortality

Many doses of MDMA were administered in clinical settings with no known instances of mortality before MDMA was first declared a Schedule I substance in 1985.[87,88] However, in recreational non-clinical settings, the risk of death for a first-time use of Ecstasy is between 1 in 2,000 to 1 in 50,000.[89,90] Out of 81 deaths of individuals who used recreational drugs and were found to have MDMA in their system at the time of death, 2 deaths per year were confirmed to

involve only MDMA.[89] All other deaths included other substances, with opiates being involved in the majority (59%) of cases.[89]

The two most common causes of death related to Ecstasy use are hyperthermia and hyponatremia,[91] both of which are a direct result of use in recreational settings characterized by high temperatures, physical exertion, and a lack of appropriately balanced fluid and electrolyte intake. Hyperthermia and hyponatremia both are preventable in controlled clinical settings. Altogether, deaths involving Ecstasy use are rarely a direct result of MDMA itself. Instead, cases of death are typically compounded by other substances, hyperthermia, hyponatremia, the environment, and/or underlying medical conditions – risks that will be directly minimized in our controlled clinical trial through careful pre-screening and assessment, using pharmaceutical-grade drug products at precise dosages without adulterants, and implementation of appropriate safeguards and precautions detailed further in the following subsections.

2.3.2 Hyperthermia

Hyperthermia (body temperature > 40°C) and its sequelae are, by far, the most common cause of morbidity and mortality related to recreational Ecstasy use, with 183 total reports in the literature.[92] All of these cases comprise individuals who used Ecstasy in non-prescribed settings. Therapeutic doses of MDMA can lead to an increase in body temperature of 0.2-0.8°C, which is typically clinically insignificant.[93] Ecstasy-related hyperthermia is thought to be multifactorial, due to a combination of high doses of MDMA, other substances, vigorous physical exertion, high ambient temperature, crowded conditions, and reduced fluid intake – all of which are commonplace in recreational settings.[94-97] The following precautions are implemented in controlled clinical settings to limit the risk of hyperthermia: MDMA is only provided at precise dosages, interacting substances are screened for, physical activity is minimal, ambient temperature is controlled, and fluids are available and frequently encouraged. With these precautions in place, there have been no known instances of clinically significant hyperthermia in clinical trials of MDMA or MDMA-AT.[1,3,4,93]

2.3.3 Hyponatremia

Hyponatremia and its sequelae are another cause of morbidity and mortality related to Ecstasy use in non-prescribed settings, with 26 total reports in the literature.[92] This is due to MDMA-induced syndrome of inappropriate antidiuretic hormone combined with voluntary compensatory overhydration, as many recreational users will overhydrate in an attempt to address the commonly known risk of hyperthermia without proper awareness of the risk of hyponatremia.[98] MDMA releases antidiuretic hormone which leads to fluid retention and decreased serum sodium concentration.[99] When this is combined with compensatory overhydration to combat dehydration, individuals can develop dangerously low sodium concentrations that can ultimately lead to seizures and death. This risk is mitigated in clinical settings by screening for electrolyte abnormalities prior to treatment and moderating fluid intake with balanced electrolyte content during treatment. With these precautions, clinically significant hyponatremia has not occurred in clinical trials of MDMA or MDMA-AT.[1,3,4,92] In addition to existing safeguards, sodium monitoring has been incorporated as a dedicated safety procedure in Section 9.9. This includes protocol-defined stopping and restarting criteria if serum sodium falls below acceptable levels or if participants become symptomatic.

2.3.4 Hepatotoxicity

Reasonable concern has been expressed over the potential for liver injury related to taking MDMA. These concerns are based on case reports and case series of individuals who used Ecstasy in non-prescribed settings. These are reasonable concerns due to the metabolism of MDMA through the liver. Cytochrome P450 2D6 (CYP2D6) is the primary metabolism route for MDMA. MDMA auto-inhibits CYP2D6 and is a competitive inhibitor of other prescription and illicit drugs metabolized by CYP2D6.[100,101] Functionally this means that subsequent doses of MDMA lead to nonlinear pharmacokinetics of both MDMA itself and other drugs. Secondarily, MDMA intoxication leads to rapid depletion of glutathione leading to free radical cytotoxicity and hepatocyte death.[102]

A 2019 review of all known cases of liver failure potentially related to MDMA between 1992 and 2015 found 32 cases of which 12 required liver transplantation and 7 resulted in death.[101] These cases are difficult to compare to clinical/research use for several reasons. Non-prescribed Ecstasy/MDMA use is often associated with settings that have high ambient temperature and high kinetic activity from the user leading to dehydration and myoglobinemia. Illicit users frequently intentionally co-ingest other substances including alcohol, cathinones (bath salts), amphetamines, ketamine, and others. Furthermore, illicit MDMA is frequently adulterated with other psychoactive substances and is subject to a wide range of potency.[100,101] In our review of clinical trials using MDMA in a controlled environment with precise dosing and monitoring, there are no reported cases of liver injury. Nevertheless, our study will go beyond what has been done in previous clinical trials by implementing additional precautions with liver function testing before and after each Dosing Session as detailed in Table 1 and Table 2 with dosing discontinuation criteria detailed in Section 9.8.1 and restart criteria detailed in Section 9.8.3.

2.3.5 Cardiovascular Conditions

Cardiovascular conditions and their sequelae are the final higher risk category of morbidity and mortality associated with Ecstasy use in non-prescribed settings, with 27 total reports of such cases in the literature.[92] However, not all cases toxicologically confirmed the presence of MDMA, and many involved other substances.[92] Similar to other amphetamines and classical psychedelics, MDMA has sympathomimetic properties that result in elevated heart rate and blood pressure[54] which can increase the risk of cardiovascular events in those with premorbid vulnerabilities.[103] In healthy individuals receiving at least 100 mg of MDMA, blood pressures remained below the hypertensive threshold of 140/90 mmHg in 95% of cases.[54,104] Risks of precipitating cardiovascular events are mitigated in controlled clinical settings through a careful pre-treatment screening with a detailed medical history and EKG, frequent blood pressure and vital sign monitoring during treatment, and ensuring blood pressure medications are available, if necessary. Our study will go one step further beyond what has been done in any past MDMA-AT study by implementing 6-lead Holter EKGs during every Dosing Session.

Since many doses of MDMA were administered in unregulated clinical settings before 1985,[87,88] at least another 1,775 individuals have received a dose of MDMA in controlled clinical research settings to date.[92] Of these, there have been no documented cases of clinically significant hyperthermia, hyponatremia, or related conditions. However, there was a single instance whereby a participant was medically observed overnight after developing chest discomfort

during his last of five MDMA sessions.[92] He had already received two blinded low dose control (30 mg initial + 15 mg supplemental dose two hours later) and two open-label high dose (125 mg initial + 62.5 mg supplemental dose two hours later) sessions of MDMA-AT with no symptoms until his fifth MDMA session. He developed chest discomfort that safely resolved after a single dose of metoprolol and overnight medical observation in a hospital setting before being discharged the next day. He was confirmed to have premature ventricular contractions (PVC), which is a benign arrhythmia that commonly can occur with exercise, caffeine, or other substances. A single PVC that was detected on his initial screening for the study had at the time been determined to be benign, and thus he was permitted to enroll. Cardiac screening criteria – to include criteria used in this clinical trial – for MDMA-AT have since become more stringent to mitigate the risk of similar cases from recurring.

$5HT_{2B}$-mediated valvular heart disease (VHD) also warrants consideration. $5HT_{2B}$ receptors are highly expressed within the fibroblasts that maintain the structural homeostasis of cardiac valves.[105] Several $5HT_{2B}$ agonist medications such as methysergide, ergotamine, and fenfluramine have been associated with VHD.[105,106] MDMA is also a $5HT_{2B}$ agonist.[107] A case-control study of 33 individuals with chronic Ecstasy use versus 29 age- and gender-matched controls found that 8 chronic Ecstasy users (28%) had VHD compared to none in the control group.[108] Those with clinically relevant VHD had a higher cumulative dose of Ecstasy (mean 943 tablets) than those without clinically relevant VHD (mean 242 tablets).[108] For comparison, a full course of treatment in clinical trials of MDMA-AT involves 2-3 MDMA sessions total.[1,3,4] Although no clinical trials administering pharmaceutical-grade MDMA have been found to lead to long-term cardiac complications including $5HT_{2B}$ VHD,[92] the potential for cardiac adverse effects must still be taken into account – especially in real-world clinical implementation where patients may eventually receive a total number of doses that are beyond what has been studied thus far in clinical trials.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing uncontrolled hypertension and monitoring blood pressure and pulse, as described in Section 5.2 Exclusion Criteria. Before and after IP administration in Dosing Sessions, the therapy team will monitor vital signs. The therapy team will attend to clinical signs and symptoms of potential rare complications of the cardiovascular effects of MDMA, such as stroke or acute myocardial infarction (AMI) during Dosing Sessions. Any symptoms such as chest pain, shortness of breath, neurological deficit or confusion or other potential indicators of end organ effects will prompt additional vital sign measurements, and intervention if appropriate. The therapy team will notify the site physician for evaluation if this occurs.

If any participant has neurological deficits, as assessed by the site physician, whether or not they are associated with hypertensive crisis, they will be monitored, as described above, and the Rapid Response Team will be immediately alerted if medically indicated. If evaluation reveals a nonhemorrhagic stroke, there will be sufficient time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines.[109,110]

If a participant experiences ischemic type chest pain, whether or not it is associated with hypertensive crisis, the study team will follow hospital protocols regarding alerting the Emergency Department (ED), facilitating transport down to the ED for further evaluation, and potentially initiating a Code Blue if the participant is unresponsive. If further evaluation reveals

that the participant has had an AMI, they will be well within the time frame required for definitive therapy.

The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous coronary intervention as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in participants who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have EKG evidence of AMI.[111] Because this clinical trial will be conducted within Walter Reed National Military Medical Center (WRNMMC), participants will be able to be quickly evaluated well within the 90-minute window, thus further mitigating potential negative impacts of a cardiac event. Any participant who experiences such medical complications during a Dosing Session will not be given another Dosing Session, unless it is approved by the Investigator, Site Physician, and the Independent Safety Monitor.

The study intervention may be discontinued based on EKG criteria (Section 9.6.5) or blood pressure criteria (Section 9.7.1). In some cases, the study intervention may be continued again if certain EKG restart criteria (Section 9.6.6) or blood pressure restart criteria (Section 9.7.2) are met.

2.3.6 Neurotoxicity

Through popular media, MDMA was once thought to "put holes in your brain." These reports reflected concerns specifically related to detrimental effects of MDMA on dopamine and serotonin neurons. However, the 2002 study[112] that formed the basis of this belief was later retracted due to the lab having been found to inject their primates with methamphetamine instead of MDMA.[113] The original findings could not be reproduced when the study was replicated with confirmed MDMA.[113]

Other animal studies have reported neurotoxic injury to a subset of serotonin neuronal axons in rodents and primates with doses of 2.5-40 mg/kg (175-2,800 mg if extrapolated to a 70 kg mammal) injected subcutaneously up to twice daily for up to four consecutive days.[114-119] However, humans in controlled clinical research settings are dosed orally approximately one month apart with therapeutic doses of approximately 1.7 mg/kg (120 mg for a 70 kg person) and with a supplemental half-dose approximately 2 hours later to prolong the peak effect.[3,4] Doses in a therapeutic range in healthy human participants in clinical research settings have been found to be unlikely to be neurotoxic to serotonergic neurons, considering no detectable effects on 5HT uptake has been measured using positron-emission tomography at these doses.[120] At concentrations closer to therapeutic levels, MDMA in fact promotes neuritogenesis and synaptogenesis – the formation of new branching and interconnections between neurons.[121]

In a study of chronic recreational users of MDMA – many of whom also used other substances and who had used recreational MDMA on approximately 228 occasions with an average dose of 386 mg – reductions in ligand binding to 5HT reuptake transporters (SERT) and reduced neuroendocrine response to tryptophan suggest reduced SERT density and neuronal function after chronic recreational MDMA use.[122] A later study found decreased SERT density only in females who had used > 50 MDMA tablets recreationally over their lifetime, but there were no statistically significant decreases in SERT density in males regardless of the amount of lifetime recreational MDMA use.[123] In this same study, females who had reported remaining abstinent

from using recreational MDMA for over one year had SERT densities that were significantly higher than females with > 50 lifetime MDMA tablets but not higher than controls.[123] Thus, chronic heavy use of MDMA in recreational settings may lead to decreases in SERT density that may be reversible and normalize over time. Participants in our study will only be dosed on three separate dosing days with a maximum dosage of 180 mg per session, which altogether has not been shown to lead to any neurological sequelae.

2.3.7 Neurocognition

The body of literature regarding the impact of Ecstasy use on neurocognitive performance is overall conflicting and has substantial methodological limitations. Many studies rely on retrospective design, unmatched controls, and cohorts confounded with polysubstance use and occasionally ongoing substance use. Conclusions that can be drawn from these studies are further limited by reliance on self-report without being able to confirm the reported identity, amount, and frequency of use of Ecstasy and other substances.

A prospective cohort study of Ecstasy-naïve individuals with new Ecstasy use found no differences in attention, working memory, visual memory, and visuospatial functioning after initiating Ecstasy use.[124] The new Ecstasy use group were found to have lower scores of verbal memory, but they were still in the normal range and not corrected for multiple testing.[124] However, no differences in verbal memory were detected when using age- and gender-matched controls.[125]

One study found that individuals actively using Ecstasy had significant impairments in various types of memory, although impairments were not associated with amount of lifetime Ecstasy use.[126] A conflicting study found memory impairments only in heavy use (≥ 80 lifetime Ecstasy tablets) compared to moderate use (< 80 lifetime Ecstasy tablets) or controls.[127] This study also found no differences between moderate use and controls in any measures of neurocognition to include executive function, working memory, planning, and cognitive impulsivity.[127]

While many studies attribute neurocognitive impairments to Ecstasy use despite being confounded by concomitant substance use, one study concluded that neurocognitive impairments were in fact not associated with Ecstasy use but rather with polysubstance use.[128]

Experimental studies administering MDMA to healthy volunteers have likewise produced no evidence for acute impairments in neurocognitive functions. Individuals under the influence of MDMA displayed no appreciable changes in inhibitory control during a Go/No-Go paradigm,[129] nor did MDMA impair selective attention as measured by a Stroop paradigm.[54]

All three clinical trials of MDMA-AT for PTSD that included a neurocognitive battery[73-75] showed no change in neurocognition after a course of treatment.[1]

Overall, the literature is equivocal in terms of the relationship between non-clinical Ecstasy use and neurocognition, given the methodological limitations inherent in such studies. However, the literature is unequivocal that MDMA-AT delivered in a controlled clinical setting has no negative effects on neurocognition.[1] Whether this relates to differences in population demographics/history, purity of the compound, adulteration with other substances, or the fact that most recreational use studies include individuals with a far greater number of lifetime ingestions remains to be elucidated.

2.3.8 Psychiatric Conditions

Depression, anxiety, and psychosis are additional potential concerns with Ecstasy in non-clinical settings compared to MDMA in controlled clinical settings. In a review of 199 case reports of non-clinical Ecstasy use, approximately 20% reported psychiatric concerns.[130] Symptoms of anxiety and depression, in particular, have been associated with non-clinical Ecstasy use.[131,132] However, anxiety and depression have a stronger association to polydrug use overall compared to any single particular substance.[133-136] The extent to which these associations can be translated from non-clinical to clinical settings is limited, given the high variability of the contents of illegally obtained Ecstasy, involvement of other substance use, usage patterns in non-clinical settings, environmental factors, and possible pre-existing psychiatric conditions prior to Ecstasy use.

A 14-year prospective study of children followed into adulthood found that individuals who had used Ecstasy in adulthood were twice as likely to have had depression or anxiety in childhood.[137] Thus, it is difficult to establish direction of causal associations between Ecstasy use and psychiatric conditions, given that individuals predisposed to psychiatric conditions may be more likely to use Ecstasy and other substances in non-clinical settings.

In clinical settings, brief anxiety reactions can occur and are often self-limited within the MDMA-AT session. However, as adverse effects, there is no difference in frequency of anxiety reactions between active and placebo groups during and after a session of MDMA-AT in controlled clinical settings.[138]

Seventeen percent (17%) of individuals receiving MDMA-AT have also been found to have an increased likelihood of low mood compared to placebo during a dosing session.[138] In contrast, there was a non-significant improvement in depression over an entire treatment course when pooling all four Phase 2 clinical trials of MDMA-AT that measured depression,[1] and significant improvements in depression were found in the first Phase 3 multi-site clinical trial.[4] Depression symptom outcomes were not reported for the second Phase 3 clinical trial.[3]

Current evidence does not indicate increased risk for suicidal ideation or behavior. In studies of MDMA-AT for PTSD, six participants had suicidal behavior and a seventh was hospitalized for suicidal ideation. However, six of the seven participants were either in the placebo arm or had not received any active MDMA.[1,3,4] Safeguards and procedures for suicidal ideation and risk behavior monitoring are further detailed in Section 9.5.1.

Symptoms of psychosis associated with Ecstasy use in non-clinical settings have been reported.[139,140] However, these cases are susceptible to the same confounds that limit the generalizability of conclusions drawn between the non-clinical use of Ecstasy and the clinical use of MDMA. There are no reported instances of psychosis due to MDMA in controlled clinical settings.[1,3,4,72-74,77,141-146] This is likely due to limiting MDMA dose ranges, ensuring a therapeutic setting, and careful medical screening and monitoring – all of which will be implemented in this clinical trial.

While there is weak evidence suggesting a positive bidirectional relationship between non-clinical Ecstasy use and psychiatric conditions such as depression and anxiety,[131,132,137] such relationships have not been observed with MDMA-AT in controlled clinical settings. Stronger evidence provided by clinical trials of MDMA-AT for PTSD suggest that for carefully screened

individuals from this patient population, anxiety and psychosis are not long-term sequelae of the treatment, depression may improve, and serious suicidality is primarily found in those who do not receive the active treatment.[1,3,4]

2.3.9 Addiction and Non-Prescribed Use

Despite primarily being serotonergic, MDMA also has mild pro-dopaminergic properties which confer at least a theoretical potential for dependence.[147] Animal studies suggest that MDMA has rewarding properties, though significantly less than other substances such as cocaine, methamphetamine, or heroin.[148-153] Chronic administration of high doses of MDMA in mice does not induce physical dependence.[154] This aligns with findings in humans that approximately three-fourths of individuals who use Ecstasy in non-prescribed settings use it less frequently than once per month, often infrequently on special occasions.[155]

While evidence for the addictive properties of MDMA is equivocal, some evidence indicates MDMA may have the potential to *treat* addiction. MDMA-AT may reduce alcohol use in patients with PTSD.[1] An open-label clinical trial of individuals with heavy alcohol use who recently completed detox suggests MDMA-AT potentially may be an effective treatment for individuals diagnosed with alcohol use disorder.[143] Our study intends to explore these findings further by evaluating for alcohol and illicit drug use with regular Timeline Follow Back questionnaires throughout the study.

In a sample of 83 patients with PTSD who received MDMA-AT, eight had reported non-prescribed use of Ecstasy between the end of their course of MDMA-AT and 12-month follow-up.[1] Of those eight, six had used Ecstasy prior to the study and thus did not constitute new use. Nearly all, including the two individuals without prior use, had attempted to self-administer Ecstasy in a non-prescribed setting for therapeutic purposes. However, additional Ecstasy use was not reported after the initial non-prescribed session, as participants reported they found it to be therapeutically ineffective without trained clinical support.

Overall, although Ecstasy is one of the most commonly used recreational substances globally,[156] the risk of dependence is low compared to other recreational substances.[65,66] The risk of future non-prescribed use after receiving MDMA in a controlled clinical setting is also low but must still be considered and mitigated.[1,145] Our study will mitigate the risk of addiction and non-prescribed use by excluding individuals who have a history of using MDMA/Ecstasy/Molly, implementing eligibility screening with urine drug screens to detect current use, and incorporating point of care urine drug screens prior to each dosing session.

2.3.10 Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening condition caused by the use of substances leading to overactivation of serotonin pathways in the central and peripheral nervous systems.[157] Serotonin syndrome and potential mortality may result from coadministration of MDMA and monoamine oxidase inhibitors (MAOIs).[158-160] However, the combination of MDMA with a serotonin reuptake inhibitor paradoxically diminishes the clinical effects of MDMA and does not lead to serotonin syndrome in either rodent models[161-163] or humans.[164] This is because the entry of MDMA into the presynaptic terminal is inhibited by serotonin reuptake inhibitors.[165] Out of 20 cases of serotonin syndrome involving confirmed or presumed MDMA reported to the FDA

since 2004, none of the cases involved MDMA as the only ingested substance.[166] All 20 cases involved other substances – the most common being amphetamines.[166] Despite the paradoxical attenuation of effects when co-administering MDMA with a serotonin reuptake inhibitor, MDMA still carries a risk for serotonin syndrome with MAOIs and other serotonergic medications.[167] This risk has thus far been successfully mitigated in clinical trials involving MDMA[166] by ensuring at least 5 elimination half-lives plus a minimum of 1 week for clinical stabilization between the last dose of a serotonergic medication and the dose of MDMA; our study will also implement these same safeguards (see Section 6.7.5 Washout Parameters and Medication Tapering).

2.3.11 Relational Safety and Therapeutic Touch

The term "relational safety" is intended to encompass the domains of potential harm and associated safeguards within the relationship dynamic between the patient and other individuals, particularly the co-therapists. MDMA-AT and other psychedelic-assisted therapies involve potential risks to relational safety that must be accounted for and mitigated to the maximum extent possible. The use of therapeutic touch in MDMA-AT and other psychedelic-assisted therapies is a generally accepted practice but an unresolved question from a scientific standpoint in terms of determining the balance between its potential benefits and harms. Additional risks to relational safety also include the heightened potential for sexual abuse,[168] interpersonal dependency, and suggestibility – all of which are discussed further in the following subsections.

In alignment with the Resilient MDMA-AT Treatment Manual, therapeutic touch is occasionally offered as a form of support during an MDMA session in a manner that is discussed with the participant beforehand. The aim is to find an individualized balance between enhancing therapeutic support while respecting the participant's boundaries and comfort. Therapeutic touch typically entails a momentary holding of the participant's hand, arm, or shoulder in a supportive manner. The pleasantness of therapeutic touch is selectively enhanced by MDMA but not by methamphetamine or placebo,[62,169] and it serves to help ground the participant through challenging moments during the medication session. While therapeutic touch may be clinically advantageous to an extent that is yet uncertain, it also comes with additional risks that must be mitigated – namely, the possibility of serious boundary violations in the form of sexual touch and abuse.

Overall, the use of therapeutic touch in MDMA-AT and other psychedelic-assisted therapies remains an open question in terms of precisely where to set the threshold of allowable therapeutic touch to optimize the balance between its potential benefits and harms. In the absence of any clinical trials designed to investigate this question, the current established threshold described above is thought to strike an optimal balance between potential benefit and harm: a momentary holding of the participant's hand, arm, or shoulder during therapeutically appropriate times with precise boundaries agreed upon between the participant and therapists beforehand, and consent re-established in real time.

2.3.12 Sexual Abuse

An important domain of relational safety with MDMA-AT – and any psychedelic-assisted therapy – is the potential for sexual abuse. Contributing factors may include a combination of readjusted therapeutic boundaries due to the acceptance of therapeutic touch, the uneven power

dynamic inherent in the therapeutic relationship, an unendorsed loosening of ethical standards on the part of the therapist, and the acute effects of the MDMA which may amplify the risks associated with each of the aforementioned factors due to the patient's acutely heightened levels of trust and emotional vulnerability. With this heightened risk to relational safety also comes a need for heightened ethical safeguards detailed further in the Treatment Manual.

There have been at least two documented instances of sexual contact related to MDMA-AT prior to 1985 when MDMA-AT was still legal in clinical settings[29] and at least one instance since then in a clinical trial in Canada.[170] The most recent incident in Canada involved a participant in an MDMA-AT clinical trial where the unlicensed male therapist initiated non-intercourse intimate physical contact with the female study participant in the form of caressing and cuddling during the MDMA session which evolved into a sexual relationship outside of the study sessions. These forms of physical contact are absolutely not permitted in the MDMA-AT manual. A civil case between the participant and co-therapists was resolved out of court in 2019 with terms that are not public.[171] Detailed accounts surrounding this incident are publicly available both from the perspective of the participant[172] and the study sponsor.[170]

While allowing therapeutic touch may present additional risks for unethical behavior, these risks are significantly mitigated in modern clinical trials by numerous layers of safeguards – several of which were not in place until the current wave of clinical trials and have since been strengthened in response to the most recent case in Canada.

2.3.13 Interpersonal Dependency

Interpersonal dependency refers to "a complex of thoughts, beliefs, feelings, and behaviors revolving around needs to associate closely with valued other people."[173] Although our review did not identify evidence of interpersonal dependency with MDMA-AT published in the peer-reviewed scientific literature, there are non-scientific reports suggestive of interpersonal dependency described by at least two MDMA-AT clinical trial participants, one of whom was described as feeling "desperately dependent on her therapists" after her course of MDMA-AT had completed.[172] Given that interpersonal dependency is both a known component of several psychiatric diagnoses and can be anticipated as a component of the natural course of treatment in traditional therapy,[174] it is yet unclear to what extent the incidence and character of treatment-emergent interpersonal dependency may differ between MDMA-AT and traditional therapy. Though the MDMA-AT treatment modality allows for interpersonal dependency and other relational dynamics to be processed as an aspect of integration therapy, further research is still needed to identify potential areas of risk for treatment-emergent interpersonal dependency and to develop strategies that may further mitigate potential harm.

2.3.14 Suggestibility

Suggestibility is "an individual's susceptibility or responsiveness to suggestion."[175] While LSD administered to healthy participants has been found to increase suggestibility,[175] MDMA has been found to not increase suggestibility in healthy participants.[176] Also, MDMA, D-amphetamine, and placebo all scored <1% of the maximum score for "impaired control and cognition" on the 5-Dimensional Altered States of Consciousness rating scale compared to 41% for LSD,[20] suggesting that cognitive control remains intact with MDMA compared to a classical psychedelic. Nevertheless, considering the attenuated fear response and enhanced prosocial

effects associated with MDMA,[177] more studies are needed to accurately profile the potential risks of suggestibility with MDMA-AT that might increase a patient's vulnerability to unintended harm. Clinical trials of MDMA-AT – to include ours – mitigates the potential harm of suggestibility by training and implementing a therapeutic modality that is fundamentally patient-centered, which ultimately means that the therapist maintains a dynamic where the participant is understood to be the expert of their experience and the therapist's role is to facilitate the therapy in a direction guided by the participant.

2.3.15 Driving Limitations

In past studies, participants have reported blurred vision (8.7%), eye wiggling (13%), pupil dilation (15.2%), feeling tired/drowsy (6.5%), or dizzy (13%) after taking MDMA. Participants should not drive or use machinery immediately after latest treatment administration until cleared by the study team, which will typically occur after the Integration Session the morning after Dosing Sessions (up to 24 hours afterwards).

2.3.16 Duty Limitations

As an Active Duty, Guard, or Reserve service member, there is a possibility that participating in this study may affect ability to perform duties. Participants are encouraged to seek guidance from their supervisor or Commander regarding duty limitations. The study team will recommend that participants be either on convalescent leave or medical TDY for 7 days (Sunday-Saturday) the week of their Dosing Sessions. Participants will be cleared to return to their duties after their convalescent leave or medical TDY the week of their Dosing Sessions, which will typically be on the 5th day after their Dosing Session.

2.3.17 Loss of 9-15 Workdays

There are no monetary expenses for participants taking part in this research study except for the loss of 9-15 workdays.

2.3.18 Emotional Discomfort

The interviews and questionnaires participants complete during the study involve no specific risks or discomforts beyond those of a standard clinical interview. Participants may feel upset at the review of emotional experiences or may feel boredom or fatigue. Answering questions about suicidality may also be upsetting. The study team will be available for support as needed.

2.3.19 Blood Draws

Participants may have a bruise or be sore at the site where blood is drawn. There is also a possibility of infection at the insertion site. Study staff will adhere to appropriate blood draw procedures to minimize any risk of infection.

2.3.20 Audio/Video Recordings

All Independent Rater, Preparatory, Dosing, and Integration sessions will be recorded. The audio/video recordings are to ensure participant safety and that therapists are adhering to the

highest standards of quality outlined in our study's procedures. There is a risk of breach of privacy; to limit this risk,audio and video recordings will be captured locally on a secure, stand-alone closed-circuit system to ensure physical isolation of the data.

2.3.21 Virtual Visits

There may be risks, including potential breach of security and technological difficulties or interruptions associated with virtual visits. To reduce these risks only secure, HIPAA-compliant, and government-approved telehealth systems will be used throughout the study.

2.3.22 Trauma Therapy

The treatment being tested in this study is a combination of a drug (MDMA) and therapy. Any therapy, including MDMA-assisted therapy, can be a challenging process when it addresses emotionally painful experiences, and symptoms may become more pronounced at times. During the study and/or after, participants may experience increased anxiety, sadness, or other difficult feelings and thoughts, including the possibility of suicidal thoughts. The study is designed to assess these experiences and provide participants support if these issues arise.

2.3.23 Reproductive Health

It is unknown to what extent MDMA may or may not impact one's sperm, unfertilized egg, unborn child, or breastfeeding child. For this reason, we ask that participants utilize approved birth control methods and not breastfeed throughout the duration of the study until the Primary Endpoint (approximately 1 month after the final Dosing Session). Participants will be disenrolled or not allowed to enroll if they cannot agree to use recommended birth control methods, become pregnant, or are breastfeeding. If pregnancy occurs while participating in the study, the participant will not undergo any additional Dosing Sessions, though they will be offered the option to finish the Integration Sessions associated with their most recent Dosing Session and will also be invited to complete Primary and Secondary Endpoint measures as well as Study Completion procedures. Any participant who becomes pregnant during the study will be monitored by the study investigator and pregnancy-related outcomes will be reported.

If participants are able to become pregnant, they will take a pregnancy test before participating in this study and the morning of each Dosing Session before they are allowed to take the study intervention. If participants become pregnant or feel they might be pregnant at any point before or during the study, they will be advised to contact their personal physician and the principal investigator of this study listed in the Contact Information section at the end of this document.

2.3.24 Buccal Swabs

Release of personally identifiable genetic information may pose a possible risk of discrimination or increased difficulty in obtaining certain types of insurance for participants and/or their family members. The Genetic Information Nondiscrimination Act of 2008 (Pub. L. 110-233) also known as "GINA" is a federal law that prohibits discrimination in health insurance coverage and employment based on genetic information. However, GINA does not apply to employers with fewer than 15 employees. GINA's protections in employment do not extend to the US military.

Nor does it apply to health insurance through the TRICARE military health system, the Indian Health Service, the Veterans Health Administration, or the Federal Employees Health Benefits Program. Lastly, the law does not cover long term care insurance, life insurance or disability insurance.

2.3.25 Simultaneous Dosing Model

Previous MDMA-AT clinical trials have relied on a two-therapist model, with both therapists present for all Preparation, Dosing, and Integration Sessions. While effective, this approach is highly resource-intensive and may limit accessibility and scalability. To evaluate a more efficient and scalable approach for real-world settings, this study will implement a Simultaneous Dosing Model. In this model, one therapist (Lead Monitor) is present in each dosing room with a participant, and up to five Dosing Sessions may occur simultaneously in five different rooms. A Supervising Monitor (a clinician) and other Assistant Monitors (can be either clinical or non-clinical study team members) will monitor all sessions in real-time from a nearby control room via a live audio-video feed. If a therapist signals the need for assistance, the Supervising Monitor or an authorized Assistant Monitor will immediately respond and provide support. Therapists will be relieved for breaks by Assistant Monitors to ensure participants are never left alone during Dosing Sessions.

This Simultaneous Dosing Model has been previously used in FDA Investigational New Drug (IND)-regulated psilocybin therapy trials for depression, with protocols approved by Institutional Review Board (IRBs) such as Advarra and the Sheppard Pratt Health System.[178,179] These studies did not identify any new safety signals compared to traditional models. Another psilocybin study in Europe that concurrently dosed up to six healthy volunteers also reported no serious treatment-emergent adverse events.[180] Although our trial will be the first to apply this model to MDMA-AT, our team has visited and consulted with both U.S. psychedelic research centers that pioneered this dosing model to incorporate best practices.

See Section 6.3 for a more detailed framework of the Simultaneous Dosing Model, to include descriptions of the various roles and responsibilities, parameters for monitoring and assistance, and additional layers of safeguards to ensure uncompromised participant safety.

2.3.26 Safety Summary of MDMA and MDMA-AT

Conclusions and preconceptions drawn from the use of Ecstasy in non-clinical settings need to be clearly distinguished from the use of MDMA in controlled clinical settings. Ecstasy in non-clinical settings can indeed be harmful and even fatal on rare occasions without appropriate precautions. In contrast, the use of pharmaceutical-grade MDMA at therapeutic dosages with appropriate precautions in clinical settings with trained professionals appears to be safe.

Risk of addiction or future non-prescribed use is low when MDMA is administered in a clinical research setting. Whether the low likelihood of future non-prescribed use changes with increased access to MDMA secondary to potential FDA approval remains to be assessed. Although chronic heavy use of recreational Ecstasy may be associated with impaired neurocognition, therapeutic MDMA in controlled clinical settings has not been found to impair neurocognition. The factors dictating these differences are currently not well understood, though impurity and unknown dosages of recreational Ecstasy almost certainly play a role. The three most common causes of

morbidity and mortality associated with non-clinical Ecstasy use are hyperthermia, hyponatremia, and cardiac conditions. However, the factors that confer an increased risk of morbidity and mortality with non-clinical Ecstasy use can be mitigated when using pharmaceutical-grade MDMA in controlled clinical settings with appropriately trained providers, proper screening and assessment, and fidelity to standard precautionary measures. MDMA-AT in FDA-approved clinical settings allows for appropriate dosing, assurance of purity, preventing physical overexertion, maintaining appropriate body temperature with a temperature-controlled environment, moderated/balanced fluid and electrolyte intake, thorough medical screening and oversight, and availability of specially trained therapists to facilitate an optimally safe and therapeutic process. When combining all these factors, MDMA-AT in an FDA-approved clinical setting with all appropriate safeguards in place appears to be medically and psychiatrically safe.

2.4 Low-dose MDMA as Control Condition

2.4.1 Justification for Low-dose MDMA as Control Condition

Maintaining participant blinding continues to pose a significant challenge in research with psychedelics—to include MDMA—due to the unique nature and intensity of their subjective effects.[181] An effective active control compound elicits similar physiologic and subjective effects on the participants and aids in mitigating participant unblinding. The FDA Advisory Committee reviewing the New Drug Application of MDMA-AT for PTSD in 2024 expressed concerns about whether issues of functional unblinding and expectancy effects may have impacted the reported efficacy of MDMA-AT in prior studies. Thus, minimizing functional unblinding will be a critical component of our study design.

Across all Phase 2 and 3 studies of MDMA-AT for PTSD that reported blinding, inactive placebo assignment was correctly guessed by up to 95% of participants and 100% of therapists.[3,4,72-74,77] To address these concerns, we will be using low-dose MDMA as the active control for this clinical trial. By using low-dose MDMA, we intend to reduce both functional unblinding and expectancy effects, as all participants would be guaranteed to receive MDMA.

Six Phase 2 trials of MDMA-AT for PTSD used low-dose MDMA as a comparator, in which assignment to low-dose MDMA was correctly guessed by up to 73% of participants and 77% of therapists. Although this represents a relative improvement in blinding over using an inactive placebo,[74,77] there still remains an opportunity to further minimize functional unblinding by further iterating upon the design of the low-dose MDMA active control condition.

A 102.5 mg total split dose (75 mg initial + 37.5 mg supplemental) was found to be a therapeutic dose with a strong effect size.[72] A 60 mg total split dose (40 mg initial + 20 mg supplemental) in an internal Lykos (now Resilient Pharmaceuticals) analysis was also found to be a potentially therapeutic dose in some individuals.[74] A small study using a total split dose of 37.5 mg (25 mg initial + 12.5 mg supplemental) reported the best blinding relative to other Phase 2 and 3 studies of MDMA-AT for PTSD, which reinforces the value of 37.5 mg total dose for the control condition. However, the subjective effects of 0.5 mg/kg (35-40 mg for a 70-80 kg person) more closely resemble inactive placebo than full-dose MDMA,[182] indicating higher peak effects may better improve blinding. This could be achieved by increasing the initial MDMA dose to be higher than 25 mg while keeping the total dose constant by reducing the supplemental dose. Furthermore, recent pharmacokinetic modeling and simulation emphasizes that total exposure

(initial plus supplemental doses) is a critical factor when predicting a minimal effective dose.[183] For these reasons, our study will use a *40 mg total dose strategy (40 mg initial + 0 mg supplemental)*. This strategy intends to increase subjective effects (and thus reduce functional unblinding, compared to 25 mg + 12.5 mg). It also intends to minimize potential therapeutic effects (our 40 mg + 0 mg strategy would have lower potential for therapeutic effect than a 40 mg + 20 mg strategy).

All participants – whether in the full-dose or low-dose MDMA conditions – will be offered two capsules for their initial dose and one capsule for their optional supplemental dose during each Dosing Session. If randomized to the low-dose MDMA condition, participants will receive one capsule containing 40 mg MDMA and a second capsule containing inactive placebo (indistinguishable weight placebo comprised entirely of mannitol and magnesium stearate). The optional supplemental dose will also contain inactive placebo. Any possibility of a participant being functionally unblinded due to the inactive supplemental dose will be mitigated by informing all participants during informed consent that each of the three capsules they receive as supplementary dose during each Dosing Session could include 0-60 mg of MDMA. Thus, even if a participant believes that their supplemental dose was inert, that will not be linked to unblinding them to their assignment to the control arm.

2.4.2 Risks of Low-dose MDMA

There is no statistically significant evidence that indicates unique risks to participants of receiving low-dose MDMA as compared to full-dose MDMA. We will be monitoring the safety of all participants for any potential signals of differential risk between study arms, including cardiac, hepatic, and psychiatric adverse effects.

2.5 Benefit Assessment

This proposed research is designed to innovate upon three main gaps in the current literature by: 1) addressing the major challenge of resource-intensiveness by implementing an emerging modality called Simultaneous Dosing, 2) evaluating potential biopsychosocial moderators of MDMA-AT treatment effect to predict treatment responders versus non-responders, and 3) evaluating MDMA-AT specifically for SMs to demonstrate improvements not only in symptoms of PTSD and psychiatric comorbidities but also functional impairment and duty status. This study is not duplicative of existing research.

A major drawback of MDMA-AT – and all other psychedelic-assisted therapies – is the resource-intensiveness. The traditional MDMA-AT protocol studied in Phase 2 and 3 trials required two co-therapists to work with the participant throughout the treatment course during each preparation, medication, and integration therapy session. This equated to approximately 42 hours per therapist per treatment course or 84 therapist-hours when accounting for both therapists. A high priority in the post-FDA-approval landscape will be increasing access to treatment by reducing resource-intensiveness without compromising safety and efficacy.

For these reasons, this study will utilize an emerging model described as Simultaneous Dosing.[178] Instead of having two co-therapists per participant, this model allows for one therapist per participant with multiple treatment rooms ongoing at the same time during medication administration to allow for a supervising therapist to monitor all treatment rooms by video feed

and provide in-person assistance when needed. Although one study of psilocybin-assisted therapy has been completed utilizing the Simultaneous Dosing model, no studies of MDMA-AT have thus far been completed with this model. This study would be the first. If Simultaneous Dosing is adopted in clinical implementation, this model will have the potential to substantially improve resource-efficiency and accessibility of MDMA-AT, meaning more patients may be able to benefit from this treatment with fewer allocated resources.

Although over two-thirds of patients who complete the lengthy course of MDMA-AT are no longer diagnosable with PTSD, that means one-third of patients still will be diagnosable. Because of the opportunity costs of a treatment non-responder delaying the treatment of another treatment responder, reliably identifying patients likely to be treatment responders versus non-responders is another top priority for improving overall clinical impact across a population of eligible patients. No moderators of MDMA-AT treatment effect have yet been identified. Our study will evaluate potential biologic moderators of treatment effect such as serum biomarkers and pharmacogenomic profile. Psychosocial-spiritual factors evaluated will include measures of emotional invalidation, treatment readiness, social support, therapeutic alliance, and spirituality. Identifying candidate biopsychosocial moderators of MDMA-AT treatment effect through this study will allow for future clinical trials that are specifically designed to validate the clinical utility of these moderators.

Though several studies of MDMA-AT[72] and other psychedelics[184] have been conducted for Veterans, no clinical trials of MDMA or any psychedelic have yet been conducted for AD SMs. Furthermore, the single completed trial of MDMA-AT for Veterans was not adequately powered to evaluate treatment efficacy.[72] Out of all of the potential treatments authorized to be studied in Section 723 of NDAA 2024, MDMA is closest to receiving FDA-approval.[185] All the other treatments mentioned are potentially 3 to over 10 years away from being considered for FDA-approval. Thus, the treatment with the most pressing need to be studied for AD SMs is MDMA-AT due to its imminent potential clinical implementation.

Section 723 of NDAA 2024 authorizes the DoD to study MDMA-AT – and other specified psychedelics – for AD SMs with either PTSD or TBI.[5] This study specifically meets the requirements of the Section 723 of NDAA 2024.[5] Independent of meeting the requirements of Section 723 of NDAA 2024, the DoD is still able to fund and conduct studies of Schedule I substances administered to SMs.[5,8] MDMA administered in the context of MDMA-AT will likely be de-scheduled from Schedule I due to its accepted medical use if it were to be FDA-approved. This will then negate the additional layer of military-specific approval requirements in Army Regulation 40-7 related to Schedule I substances administered to SMs.[8]

PTSD is the most common *psychiatric* diagnosis for medical discharge in all branches, and it is the most common diagnosis (*medical or psychiatric*) for medical discharge from the Army.[18] Approximately 6,000-8,000 SMs are medically discharged from the military with PTSD annually, most of whom with combat experience.[18,19] The accelerated loss of SMs with combat experience is further troublesome in the larger context of recruitment shortfalls and now limited opportunities for SMs to gain new combat experience. Thus, at least from the perspective of net combat experience still on AD as one marker of readiness, overall force readiness may be gradually decreasing unless more measures are implemented to mitigate these losses. Considering the current best first-line treatments for PTSD lead to loss of diagnosis in 28-40% of

military-related PTSD,[2] implementing more efficacious treatments for PTSD is a major opportunity to improve force readiness.

In summary, not only is MDMA-AT highly efficacious for PTSD over the short-term with 67-71% no longer being diagnosable after a course of treatment,[3,4] but the long-term treatment effects also continue to improve after 1 year[1] and remain durable with 74% no longer diagnosable nearly 4 years later.[10] Furthermore, current antidepressant medications which are currently second-line treatments for PTSD require continuous daily treatment to maintain their low to moderate efficacy.[1] Whereas with MDMA-AT, a patient will only receive MDMA on three separate days, each one month apart, and thus will not need any continuous treatment to maintain its high efficacy. A high efficacy definitive treatment that does not need ongoing intervention to maintain its efficacy is precisely what SMs need to avert premature medical discharge for PTSD, especially in the context of inadequate alternative treatments for PTSD. If the favorable profile of safety and efficacy for MDMA-AT can be replicated in the military population, MDMA-AT may eventually be offered clinically after less resource-intensive first-line treatments like PE and CPT have failed for a particular SM. If safety, efficacy, and durability of MDMA-AT can be validated for SMs, we may be able to avert more premature medical discharges and retain more SMs on active duty along with their valuable military experience which in turn may directly improve force readiness.

3 Objectives

The overall objective for the study is to determine the safety, efficacy, and durability of delivering MDMA-Assisted Therapy through a Simultaneous Dosing Model for military Service Members to reduce symptoms of PTSD and associated comorbidities, as compared to the same therapy combined with low-dose MDMA.

Table 6. Objectives and Measures

Objectives	Measures
Screening/Eligibility	
Confirm PTSD diagnosis and screen for psychiatric comorbidities.	MINI
Screen for comorbid personality disorders.	SCID-5-SPQ and SCID-5-PD
Screen for PTSD diagnosis and severity.	PCL-5 with LEC-5
Primary	
Determine treatment efficacy by comparing between-group changes in PTSD symptom severity from baseline to primary endpoint at 1 month after third dosing session.	CAPS-5-R
Secondary	
Determine durability of treatment efficacy by comparing between-group changes in PTSD symptom severity from primary endpoint to secondary endpoint.	CAPS-5-R

Objectives	Measures
Determine between-group differences in functional disability from baseline to primary endpoint.	WHODAS 2.0
Determine durability of between-group differences in functional disability between primary endpoint and secondary endpoint.	WHODAS 2.0
Describe the number of simultaneously overlapping Support Events (when a study team member enters the dosing room to provide assistance) per study arm and combined overall.	Support Event Reporting Form
Safety	
Describe change in ΔQTc_{Max} (QTc at 2 hours and 4 hours post-dosing versus baseline) for each dosing session by treatment group.	ΔQTc_{Max} per Holter Monitor EKG
Describe the frequency of events of $\Delta QTc_{Max} > 60$ ms for each dosing session by treatment group.	ΔQTc_{Max} per Holter Monitor EKG
Describe the frequency of events of $QTc_{Max} > 500$ ms for each dosing session by treatment group.	QTc_{Max} per Holter Monitor EKG
Describe the frequency of arrhythmias identified via Holter monitor EKG during each dosing session by treatment group.	Holter Monitor EKG
Describe changes in vital signs from pre-IP administration to 2 hours post-dosing, 4 hours post-dosing, and end of each Dosing Session for Dosing Sessions at initial doses of 40, 80, and 120 mg of MDMA.	Blood pressure, heart rate, and body temperature
Describe hepatic functioning before and after each Dosing Session with initial doses of 40, 80, and 120 mg of MDMA.	ALT, AST, ALP, and total/direct/indirect bilirubin
Describe the frequency of meeting drug-induced liver injury stopping criteria after Dosing Sessions by treatment group.	ALT, AST, ALP, and total/direct/indirect bilirubin
Describe the frequency of meeting close observation for liver injury criteria after Dosing Sessions by treatment group.	ALT and AST
Describe the frequency of disposition outcomes (continued enrollment vs study withdrawal) after meeting close observation for liver injury criteria after Dosing Sessions by treatment group.	Liver Injury Reporting Form
Describe sodium and potassium levels before and after each Dosing Session by treatment group.	BMP
Describe the frequency of AEs by maximum severity across both study arms as well as during and after each Dosing Session at initial doses of 40, 80, and 120 mg of MDMA.	AEs reported in eCRF

Objectives	Measures
Describe the frequency of AEs by maximum severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, continuing at primary endpoint, or continuing at secondary endpoint by treatment group.	AEs reported in eCRF
Describe the frequency of Treatment Emergent AEs (TEAEs), by relation to IP in the full-dose vs low-dose MDMA arms.	AEs reported in eCRF
Describe the frequency of TEAEs by maximum severity reported during a Dosing Session and at each Integration Session in the full-dose vs low-dose MDMA arms.	AEs reported in eCRF
Describe the frequency of SAEs in the full-dose vs low-dose MDMA arms.	SAEs reported in eCRF
Describe the frequency of positive or serious ideation and suicidal behavior in the full-dose vs low-dose MDMA arms.	C-SSRS (Since Last Month & Since Last Visit)
Describe the frequency of illicit substance use in the full-dose vs low-dose MDMA arms.	Drug Use Questionnaire (Baseline and Follow-up Versions)
Describe the number of simultaneous Support Events per study arm and combined overall, and by minimum Monitor training level required per event.	Support Event Reporting Form
Describe the number and nature of simultaneous dosing Support Events categorized as Emergent, Urgent, or Routine Therapist events and Emergent, Urgent, or Routine Participant events.	Support Event Reporting Form
Describe the time between therapist-initiated Support Event requests and the supporting Monitor entering the room.	Support Event Reporting Form
Describe the number of Support Events that required ≤ 5 minutes and > 5 minutes for the supporting Monitor to enter the room by treatment arm.	Support Event Reporting Form
Characterize reported barriers to a quicker response for each Support Event that took > 5 minutes for the supporting Monitor to enter the room as well for all Support Events overall.	Support Event Reporting Form
Characterize frequency and duration of Support Events per study arm and overall.	Support Event Reporting Form
Characterize what qualitative interventions, if any, were provided by the supporting Monitor during a Support Event by treatment arm.	Support Event Reporting Form
Assess the feasibility of a Non-clinical Assistant Monitor temporarily monitoring participants for low-risk Support Events by characterizing any corresponding AEs during these events.	Support Event Reporting Form

Objectives	**Measures**	
Assess the feasibility of a Non-clinical Assistant Monitor temporarily monitoring participants for low-risk Support Events by evaluating the incidence of a Clinical Assistant Monitor or Supervising Monitor needing to enter the room during these Support Events.	Support Event Reporting Form	
Exploratory		
Describe response, loss of diagnosis, and remission of PTSD symptoms compared between groups from baseline to primary and secondary endpoints.	CAPS-5-R	
Compare PTSD severity after each Dosing Session between groups.	PCL-5	
Describe treatment tolerability as measured by rates of dropout due to AE intolerability throughout study period between groups.	Dropout Rates	
Assess treatment acceptability using acceptability scores from a questionnaire conducted during the follow-up phase in the treatment group.	TFA	
Analyze participants' qualitative experiences and feedback.	Qualitative Interview	
Evaluate between-group differences in the following domains between baseline and primary endpoint as well as durability of differences between primary and secondary endpoint.	Comorbid Depression	BDI-II
	Suicidality	C-SSRS (Lifetime, Since Last Month, Since Last Visit)
	Sleep Disturbance	PSQI
	Moral Injury	MIOS
	Quality of Life	WHOQOL-BREF
	Burden of absenteeism and presenteeism	HPQSF
	Alcohol Use	TLFB
	Nicotine Use	STUQ
	Neurocognition	NIH Toolbox
	Headache	HIT-6
	Pain	PEG
Assess the indicated biopsychosocial variables as potential moderators of treatment response for PTSD severity.	Comorbid Traumatic Brain Injury	OSU TBI Inventory

Objectives	**Measures**	
	Adverse Childhood Experiences	ACE
	Expectancy	SETS
	Blast Exposure	BETS
	Beliefs about Mental Health Treatment	EASI-BAMHT
	Drug Use Desire and Intent	DUDIQ
	Treatment Readiness	PPS
	Social Support	MSPSS
	Therapeutic Alliance	WAI-SR
	Life Events History	LEC-5
	Alcohol-Related Problems	AUDIT
	Drug-Related Problems	DUDIT
	Psychological Flexibility	MPFI-24
	Self-Compassion	SCS
	Reaction to Touch	RTM
	Thwarted Belongingness & Perceived Burdensomeness	INQ-15
	Modified Drug Effects	mDEQ-3
	Euphoria	EA-Pre, EA-Post
	Study Blinding	Blinding Survey
	Pharmacogenomic Profile	Genomind Cheek Swab
Characterize between-group changes in fitness for duty by evaluating monthly differences between baseline and follow-up phases.	Medical Profile Status (none, temporary, or permanent) or Limited Duty Status	

Objectives	Measures
Describe utilization of psychotherapy and psychiatric medication by group between primary and secondary endpoints.	Medication Reconciliation and Follow-up Questionnaire
Characterize short-term changes in EEG signal pre versus during Dosing Session.	Neurable EEG Headphones
Characterize short-term changes in EEG signal pre versus 1 day post Dosing Session.	Neurable EEG Headphones
Characterize changes in EEG biomarkers observed 1 day post Dosing Session versus 1 day prior to the next Dosing Session.	Neurable EEG Headphones

Abbreviations: ACE, Adverse Childhood Experiences Questionnaire; AE, adverse event; AUDIT, Alcohol Use Disorders Identification Test; BDI-II, Beck Depression Inventory-II; BETS, Blast Exposure Threshold Survey; BMP, Basic Metabolic Panel; CAPS-5-R, Clinician-Administered PTSD Scale for DSM-5 Revised; CAM, Confusion Assessment Method; C-SSRS, Columbia-Suicide Severity Rating Scale; DUDIQ, Drug Use Desire and Intent Questionnaire; DUDIT, Drug Abuse Disorders Identification Test; DUQ, Drug Use Questionnaire; EA-Pre, Euphoria Assessment Pre-Dosing; EA-Post, Euphoria Assessment Post-Dosing; EASI (BAMHT Scale), Endorsed and Anticipated Stigma Inventory; eCRF, electronic case report form; EEG, electroencephalography; EN, enrollment; F_1, follow-up safety phone call; HIT-6, Headache Impact Test 6; HPQSF, Health and Work Performance Absenteeism and Presenteeism Short Form; I_n, integration session #n; LEC-5, Life Events Checklist; mDEQ-3, Modified Differential Emotions Scale; MINI, Mini International Neuropsychiatric Interview; MIOS, Moral Injury Outcome Scale; MPFI-24, Multidimensional Psychological Flexibility Inventory-24; MSPSS, Multidimensional Scale of Perceived Social Support; MT, medication taper phone call; NIH, National Institutes of Health; OSU-TBI, Ohio State University Traumatic Brain Injury Identification Method; PCL-5, PTSD Checklist for DSM-5; PEG, Pain, Enjoyment of Life and General Activity Scale; PIES, Perceived Invalidation of Emotion Scale; PPS, Psychedelic Preparedness Scale; INQ-15, Interpersonal Needs Questionnaire; PSQI, Pittsburgh Sleep Quality Index; R, randomization; RTM, Reactions to Touch Measure; SCID-5-PD, Structured Clinical Interview for DSM-5 Personality Disorders; SCID-5-SPQ, SCID-5 Self-report Personality Questionnaire; SETS, Stanford Expectations of Treatment Scale; SCS-SF, Self-Compassion Scale Short Form; STUQ, Smoking and Tobacco Use Questionnaire; TFA, Theoretical Framework of Acceptability; TLFB, Timeline Follow-Back Calendar, Alcohol; WAI-SR, Working Alliance Inventory-Short Revised; WHOQOL, World Health Organization Quality of Life; WHODAS 2.0, World Health Organization Disability Assessment Schedule.

See Table 5 for Assessment Timepoints.

4 Study Design

4.1 Overview

The study design is a randomized, double-blind, active-controlled, two-arm, single-site, Phase 2 clinical trial to evaluate MDMA-AT for SMs with PTSD in an MHS setting. Initially, five participants will receive open-label, full-dose MDMA-AT to establish the therapists' adherence to study protocols during an open-label lead-in training cohort. 86 participants will be randomized to MDMA-AT with either full-dose or low-dose MDMA. The therapy will integrate Acceptance and Commitment Therapy as a therapeutic modality. Participants will be recruited locally from MHS clinics in the National Capital Region and non-locally throughout the MHS to examine the feasibility, tolerability, and acceptability of the anticipated regional referral center model. Notable inclusions are an active diagnosis of moderate to severe PTSD (PCL-5 ≥38); command concurrence that the SM is not anticipated to be deployed again within the next two years; and status as Active Duty, Guard, or Reserve. Notable exclusions include uncontrolled hypertension, elevated QTc > 450 ms, psychotic spectrum disorders, borderline personality

disorder, and any life-time history of using MDMA. The full list of all inclusion and exclusion criteria can be found in Sections 5.1 Inclusion Criteria and 5.2 Exclusion Criteria.

For each participant, the study will consist of:

- **Screening Phase**: Phone screen, screening informed consent, medical screening, study information consent, eligibility assessments, and enrollment of eligible participants. See Section 8.1 Screening Phase for more information.
- **Preparation Phase with Enrollment Confirmation**: Medication tapering, three 90-minute Preparatory Sessions, and baseline assessments leading to enrollment confirmation. See Section 8.2 Preparation Phase for more information.
- **Intervention Phase**: Three month-long intervention cycles, each of which will involve a 6-8 hour Dosing Session and three subsequent 90-minute non-drug Integration Sessions. In total, the Intervention Phase should last approximately 12 weeks. See Section 8.4 Intervention Phase for more information.
- **Follow-up Phase with Primary and Secondary Endpoints:** Primary Endpoint which is one month after the final Dosing Session, four monthly safety follow-up phone calls, and Secondary Endpoint three months after the final Dosing Session. See Section 8.5 Follow-up Phase for more information.
- **Study Completion:** Study Completion will occur after all measures and procedures are completed at the Secondary Endpoint three months after the final Dosing Session. See Section 8.6 Study Completion for more information.

4.2 Open-Label Lead-in Training Cohort

The study will incorporate an open-label lead-in training cohort for up to 10 study therapists working with 5 participants. The primary purpose of this cohort is to act as a quality assurance measure by ensuring fidelity to study procedures for study team members and to provide training for therapists prior to each therapist proceeding to randomized participants.

All study design and procedures will be identical between the open-label and randomized cohorts, with the following exceptions for the open-label cohort:

- All Preparation, Dosing, and Integration Sessions will involve two co-therapists present in each session.
- No randomization or blinding procedures will occur. The participant and all study team members will be unblinded and have a fully transparent understanding that the participant is being dosed with full-dose MDMA.

From the perspective of each study therapist, the open-label training cohort will always occur first prior to initiation of the randomized cohort, with the two cohorts occurring in sequence (Figure 2). However, from the perspective of the overall study, overlap between the open-label and randomized cohorts is permitted, with the two cohorts occurring in parallel (e.g., one therapist who has finished their open-label participant may already be working with randomized participants, while another therapist may still be working with an open-label participant).

For example, if all available therapists have been fully trained and their adherence to study procedures has been established after fewer than five open-label participants, the randomized period may begin without all five open-label participants having been enrolled. This will allow

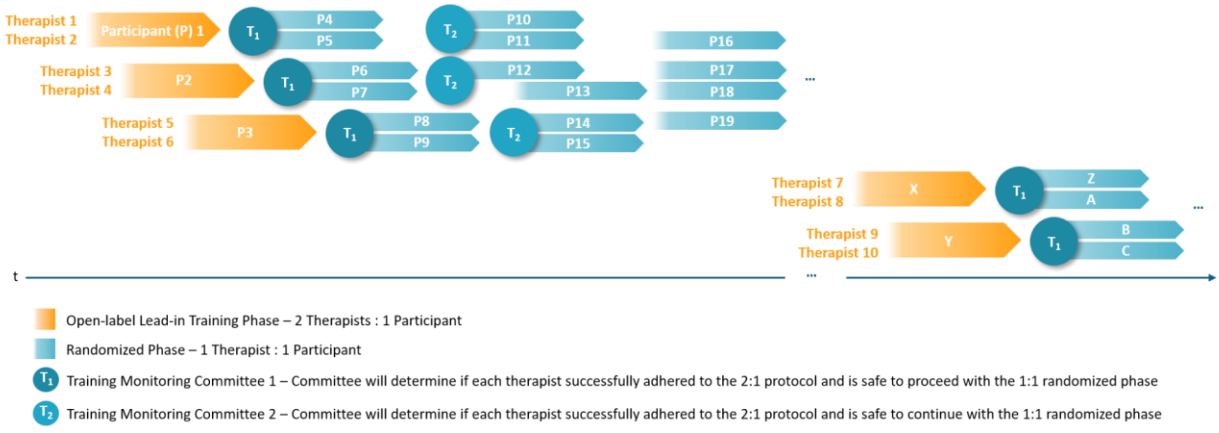
for therapists who are on-boarded at a later date to also be trained via an open-label participant. This will also allow for a therapist to be retrained with greater oversight if it is deemed that retraining a therapist is necessary.

4.3 Training Monitoring Committee

A Training Monitoring Committee (TMC) will determine if each study therapist is qualified to proceed from the open-label training cohort to randomized cohort after evaluating the therapist working with the first open-label participant (T1 in Figure 2). The TMC will also determine if each study therapist is qualified to continue with the randomized cohort after the therapist's first randomized participant (T2 in Figure 2).

The TMC will be composed of 1) the Principal Investigator (PI) or clinician delegate, 2) a subject matter expert in psychedelic assisted therapy, and 3) a subject matter expert in Acceptance and Commitment Therapy (ACT). Training Monitoring Committee (TMC) will review therapy sessions synchronously or asynchronously and rate study therapist fidelity in implementing the study intervention and research procedures. TMC will first assess study therapists while providing the study intervention with open label participants to ensure therapist ability to provide the study intervention with a co-therapist (two therapists per participant; T1 in Figure 2). Once approved by the TMC, the study therapist will be assessed while providing the study intervention with randomized participants to ensure their ability to provide the study intervention without a co-therapist (one therapist per participant; T2 in Figure 2). The determination at T1 will be decided by a majority determination by the TMC (two or more committee members approving the therapist). The determination at T2 will be decided by a designated TMC member. TMC members will utilize a checklist of study interventions and research procedures to assess study therapists. TMC will determine if study therapists obtain no less than 90% checklist adherence and, in their clinical judgment, are implementing the study intervention and research procedures appropriately. If indicated by the TMC, additional training and assessment will be provided to study therapists to ensure fidelity with study intervention and research procedures.

Figure 2. Open-Label Lead-in Training Cohort and Randomized Cohort



4.4 Dosing Strategy

Similar MDMA doses to those proposed in this study have been safely used in previous Phase 2 and Phase 3 studies sponsored by MAPS/Lykos (now Resilient Pharmaceuticals). Phase 2 studies indicate that 75, 100 and 125 mg MDMA initial doses with the supplemental dose provide a therapeutic effect in two to three Dosing Sessions. In Phase 2 studies, there was a -36.4 point mean change in CAPS-4 scores among active dose participants receiving two Dosing Sessions (N=72) compared to a -44.2 point mean change after three Dosing Sessions (N=51).[1] Although uncontrolled, the additional 7.8 point mean reduction observed after three Dosing Sessions compared to two, along with the observed favorable safety profile formed the basis for selection of a 3-session treatment package.

A flexible dosing regimen has been explored previously in Phase 2 studies, where participants who received doses of 0 mg to 75 mg MDMA in the blinded portion of the study crossed over to receive open-label 100 mg MDMA in the first Dosing Session with an option to increase to 125 mg MDMA in the second and third Dosing Sessions. In the opinion of the participants and therapy teams administering this treatment in Phase 2 studies, this flexible dosing regimen and three Dosing Sessions produced an optimal treatment response. Larger doses have been administered safely in a Phase 2 study (150 mg and 75 mg supplemental) and in a Phase 1 study (150 mg and 160 mg). Altogether, the results of these Phase 2 studies led to the selection of 80 mg and 120 mg MDMA as the initial active doses to be compared to inactive placebo in the Phase 3 trials.

The two Phase 3 trials involved a flexible dosing regimen across three Dosing Sessions. During the Dosing Sessions, the participant orally self-administered 2-3 capsules initially with 1 optional half-dose supplemental capsule 2 hours later. The 1st Dosing Session always involved 2 capsules for the initial dose (80 mg MDMA or inactive placebo); whereas the 2nd and 3rd Dosing Sessions allowed the participant to come to a shared decision with the study team whether to increase the initial dose to 3 capsules (120 mg or inactive placebo) plus a supplemental half-dose 2 hours later. With few exceptions, the participants almost always elected for the higher dose for the subsequent Dosing Sessions.

In our study, capsules will all contain either full-dose MDMA, low-dose MDMA, or inactive placebo (if in the active control group) depending on randomization. During the Dosing Sessions, the participant will orally self-administer an initial dose of 2 capsules and an optional supplemental dose of 1 capsule 2 hours later (±15 minutes). The 1st Dosing Session will involve self-administration of 2 capsules initially and an optional 1 capsule 2 hours later (80 mg initial + 40 mg supplemental for full-dose MDMA arm, or 40 mg initial + 0 mg supplemental for low-dose MDMA arm). The 2nd Dosing Session will also involve self-administration of 2 capsules initially and an optional 1 capsule 2 hours (±15 minutes) later (120 mg initial + 60 mg supplemental for full-dose MDMA arm, or 40 mg + 0 mg supplemental for low-dose MDMA arm). The 3rd Dosing Session will allow for the participant and study team to come to a collaborative shared decision on whether to undergo the same dosing strategy as either the 1st or 2nd Dosing Session, based on a combination of factors to include response, AE profile, and tolerability of the previous two dosing sessions.

A flexible dosing regimen was chosen to mimic anticipated clinical practice and better adapt to risk-benefit considerations. The initial full doses of 80 and 120 mg MDMA as well as 40 mg low-dose MDMA are expected to produce all commonly reported effects. The supplemental dose

in the full-dose arm will prolong subjective effects of the study drug without producing physiological effects much greater than peak effects occurring after the initial dose, and will be administered unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications. If an AE requiring medical attention occurs between the initial and supplemental dose, this will be evaluated as a potential tolerability issue by the site physician. If a participant prefers not to take the supplemental dose, the reason will be documented.

Total amounts of full-dose MDMA to be administered per Dosing Session (including supplemental dose) range from 80 to 180 mg, which align with previous studies. The total amount of low-dose MDMA to be administered per Dosing Session (including supplemental dose) is 40 mg.

Table 7. Dose Regimen of MDMA HCl

Arm	Dosing Session	Initial Dose of MDMA HCl	Supplemental Dose of MDMA HCl*	Min-Max Cumulative Dose of MDMA HCl
Full-Dose MDMA	1st	80 mg	40 mg	80 mg to 120 mg
	2nd	120 mg	60 mg	120 mg to 180 mg
	3rd	80 mg or 120 mg**	40 mg (if 80 mg initial) or 60 mg (if 120 mg initial)	80 mg to 180 mg
	Total Cumulative Dose			280 mg to 480 mg
Low-Dose MDMA	1st	40 mg	0 mg	40 mg
	2nd	40 mg	0 mg	40 mg
	3rd	40 mg	0 mg	40 mg
	Total Cumulative Dose			120 mg

*Unless tolerability issues emerge with the initial dose or the participant declines. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications

**Dose of 3rd Dosing Session based on collaborative shared decision-making between participant and study team. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications

4.5 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the trial globally.

The sponsor has the right to discontinue this study at any time. If the trial is prematurely terminated, the investigator is to promptly inform participants and will ensure they receive appropriate therapy, follow-up, and Study Exit Plan. If the study is prematurely discontinued, all procedures and requirements pertaining to retention and storage of documents will be observed. All other study materials will be returned to the sponsor and will be treated in accordance with federal and state regulations.

5 Study Population

Participants will be Active Duty, Guard, or Reserve service members in the US military with PTSD. Five (5)participants will receive open-label, full-dose MDMA-AT to establish the therapists' adherence to study protocols during an open-label lead-in training cohort. Eighty-six (86) participants will be randomized to MDMA-AT with either full-dose or low-dose MDMA.

5.1 Inclusion Criteria

5.1.1 Participant Characteristics

1. Positive endorsement of at least 1 index trauma on the LEC-5.
2. Have a PCL-5 total score of 38 or greater at screening.
3. Meet DSM-5-TR criteria for current PTSD per Mini International Neuropsychiatric Interview (MINI) at screening with a symptom duration of 6 months or longer.
4. Meet criteria for PTSD diagnosis per CAPS-5-R with a score of 26 or greater.
5. Are at least 18 years old at the time of enrollment.
6. Weigh greater than 48 kilograms.
7. Are able to swallow pills.
8. Are fluent in speaking, reading, and comprehending English.
9. Must agree to inform the investigators within 48 hours of any new medications, medical conditions, and procedures.
10. Females of childbearing potential must have a negative pregnancy test at study entry and prior to each Dosing Session and must agree to use adequate birth control for the duration of the study until at least 30 days after the final dosing session. Adequate birth control methods include intrauterine device (IUD), injected, implanted, intravaginal, or transdermal hormonal methods, abstinence, oral hormones plus a barrier contraception, vasectomized sole partner, or double barrier contraception. Two forms of contraception are required with any barrier method or oral hormones (i.e. condom plus diaphragm, condom or diaphragm plus spermicide, oral hormonal contraceptives plus spermicide or condom). Non-childbearing potential is defined as permanent sterilization, postmenopausal, or assigned male at birth.
11. Males must agree to use adequate birth control for the duration of the study until at least 30 days after the final dosing session. Adequate birth control methods for males include double barrier contraception (condom with spermicidal gel or foam), surgical sterility (defined as a vasectomy at least 3 months prior to the screening visit), or abstinence.
12. Must agree to refrain from sperm, egg, blood, and bone marrow donations for at least 30 days after the final dosing session.
13. Must have a 12-lead electrocardiogram (EKG) with QTc < 450 ms and no clinically significant abnormalities, as determined by a cardiologist.

5.1.2 Consent

14. Are able to demonstrate comprehension of consent form and study instructions, and provide informed consent.
15. Agree to have study visits recorded, including Dosing Sessions, Independent Rater assessments, and non-drug therapy sessions.

16. Must provide an emergency contact (relative, spouse, close friend, or other support person) who is willing and able to be reached by the investigators in the event a participant is imminently unsafe or unreachable.
17. Agree to the following lifestyle modifications (described in more detail in the Informed Consent Form): comply with requirements for fasting and refraining from certain medications prior to Dosing Sessions; not participate in any other interventional clinical trials during the duration of this study without prior approval of the Independent Safety Monitor; remain overnight at the study site or have an identified support person that can remain with the participant and escort them to the therapy session the day after each dosing; and commit to medication dosing, therapy, and study procedures.

5.1.3 Military-Specific

18. Must be Active Duty, National Guard, or Reserve in the United States military.
19. Must receive approval from their command to participate in the study.
20. Must be DEERS eligible.

5.2 Exclusion Criteria

5.2.1 Psychiatric

1. History of or current primary psychotic disorder to include Schizophrenia, Schizoaffective Disorder, or Bipolar Disorder 1 assessed via MINI or clinical evaluation.
2. Current Major Depressive Disorder with Psychotic Features assessed via MINI or clinical evaluation.
3. Current eating disorder with active purging assessed via MINI or clinical evaluation.
4. Current Borderline Personality Disorder assessed via SCID-5-PD or clinical evaluation.
5. Any of the following findings on Screening C-SSRS:
    a. Suicidal ideation score of 5 within the last month
    b. Suicidal ideation score of 4 or greater in the last month at a frequency of once per week or more
    c. Any suicidal behaviors within the last 3 months. The exception is that non-suicidal self-injurious behavior is not exclusionary if approved by the PI.
6. Current high suicide risk or is likely to require psychiatric hospitalization, as determined through C-SSRS, clinical interview, or clinical judgment of the investigator. Distant history of suicide attempts without current high suicide risk factors is not exclusionary.
7. Current severe substance use disorder (6 or more criteria per MINI) *not* in sustained remission (criteria not met for past 12 months) at time of enrollment. I.e., severe substance use disorders may only be included if in sustained remission. Tobacco/nicotine use disorders may be included regardless of severity.
8. Current moderate substance use disorder (4-5 criteria per MINI) *not* in early remission (criteria not met for past 3-12 months) or sustained remission (criteria not met for past 12 months) at time of enrollment. I.e., moderate substance use disorders may only be included if in early or sustained remission (criteria not met for 3 or more months). Tobacco/nicotine use disorders may be included.
9. For any illicit or prescribed substance: current substance use disorder of *any* severity, *not* in sustained remission (criteria not met for past 12 months). I.e., substance use disorders

of any severity with illicit or prescribed substances may only be included if in sustained remission.
10. Any urine drug testing during screening or enrollment that is confirmed positive for a non-prescribed substance, and the result cannot be better explained as a false positive due to another concomitant prescribed medication or proven dietary practice.
11. Have current or history of psychiatric diagnoses or symptoms that may negatively affect study participation.

5.2.2 Medical

12. Clinically significant abnormalities on screening 12-lead EKG or 1-minute 12-lead rhythm strip that precludes administration of MDMA, stimulants, or sympathomimetics, as determined by a cardiologist.
13. Two or more premature ventricular contractions (PVCs) on 1-minute rhythm strip. 1-minute 12-lead rhythm strip will be obtained when there are one or more PVCs on screening EKG or when indicated by a cardiologist.
14. Resting QTc ≥ 450 ms.
15. History of drug-induced QTc prolongation.
16. Inability to hold or discontinue concomitant medications that significantly prolong the QTc interval.
17. Clinically significant cardiac or cardiovascular abnormalities, including history of myocardial infarction, unexplained exertional syncope, Torsade de Pointes, congenital long QT syndrome, hypertrophic cardiomyopathy, congestive heart failure, family history of Long QT Syndrome, persistent atrial fibrillation, symptomatic valvular heart disease, asymptomatic severe aortic stenosis, asymptomatic severe mitral stenosis, history of diagnosis of aortic dissection or asymptomatic aortic aneurysm > 4.5 cm at the sinus of Valsalva, or history of untreated angina pectoris or unrevascularized coronary stenosis > 70%.
18. Current clinically significant electrolyte abnormalities, to include hyponatremia and hypokalemia.
19. Has clinically significant abnormal laboratory results during screening that indicate impaired liver function, to include ALT or AST >2x ULN or Total bilirubin >1.5 mg/dL unless history of Gilbert's Syndrome
20. Renal disease defined as eGFR <45 mL/min/1.73m² or creatinine >2.0 mg/dL, end-stage kidney disease, dialysis, history of renal transplant, clinically significant or progressive renal disease deemed to increase risk, or recent/unstable renal function consistent with acute kidney injury at screening. Participants with eGFR 45–59 mL/min/1.73m² may be eligible only if renal function is stable and cleared by the study physician.
21. Uncontrolled essential hypertension defined as blood pressures of greater than 140/90 mmHg assessed on three separate occasions. May have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if additional screening is passed to rule out underlying cardiovascular disease.
22. Uncontrolled hypothyroidism. May have hypothyroidism if taking adequate and stable thyroid replacement medication.
23. Type 2 Diabetes Mellitus with comorbid cardiovascular disease. May have a history of or current Type 2 Diabetes Mellitus if additional screening measures rule out underlying

cardiovascular disease, if the condition is judged to be stable on effective management, and with approval by the Independent Safety Monitor.
24. Glaucoma without approval from an ophthalmologist. May have a history of, or current, glaucoma if approval for study participation is received from an ophthalmologist.
25. History of any medical condition that could make receiving a sympathomimetic drug harmful because of increases in blood pressure and heart rate. This includes, but is not limited to, a history of cerebrovascular disorders (cerebrovascular accident, aneurysm, arteriovenous malformations, or carotid stenosis). Participants with other mild, stable chronic medical conditions may be enrolled if the study physician and Independent Safety Monitor agree the condition is unlikely to confer a significant additional health risk with administration of MDMA. This includes conditions such as gastroesophageal reflux disease and chronic low back pain.
26. Current medical diagnoses or physical health symptoms that may negatively affect study participation.

5.2.3 Other

27. Report any prescribed or non-prescribed lifetime personal use history of MDMA, 3,4-methylenedioxymethamphetamine, midomafetamine, “Ecstasy,” “Molly,” “Mandy,” or “Adam.”
28. Lack adequate social support, in the judgement of the PI.
29. Unable to safely taper off prohibited concomitant medications.
30. Are pregnant or nursing, or are able to become pregnant and are not practicing an effective means of birth control.
31. Have any current or anticipated problem which, in the opinion of the PI or Independent Safety Monitor, may interfere with study participation.

5.3 Lifestyle Modifications

All participants must agree to the following lifestyle modifications at enrollment and throughout the duration of the study. Participants are eligible to enroll in the study if they:

- Commit to fully engage in each scheduled study visit and activity to include all Preparation Sessions, Dosing Sessions, Integration Sessions, phone calls, and study measures.
- Agree to not participate in any other interventional clinical trials during the duration of this study.
- Agree to follow healthy diet, sleep, and self-care behaviors to the best of their ability.
- Agree to review and commit to abide by all Pre-dosing Instructions
- Agree to review and commit to abide by all Post-dosing Instructions

The Pre/Post-Dosing Instructions (see Section 8.3.1 Pre-Dosing Instructions and Section 8.3.2 Post-Dosing Instructions) will be provided to the participant upon completing the study informed consent. The Pre/Post-Dosing Instructions will then be reviewed with the participant at the following encounters: Preparation Sessions 1, 2, and 3; Integration Sessions 1.2, 1.3, 2.2, and 2.3.

5.4 Recruitment Strategies

Participants will be recruited from:

- WRNMMC (Local)
  - Adult Outpatient Behavioral Health
  - Adult Partial Hospitalization Program
  - Psychiatric Inpatient Services
    - 7W Inpatient Psychiatry
    - 7E Neuropsychiatry
    - Psychiatric Consult Liaison Service
- ATAMMC (Regional)
  - Adult Outpatient Behavioral Health Clinic
  - Intensive Outpatient Program
- Fort Meade (Regional)
  - Outpatient Behavioral Health Clinic
- Partner Organizations (Non-Local)
  - USSOCOM Warrior Care Program
  - Military and Veteran-related Non-Profit Organizations
  - Other MHS Mental Health-related groups

Participants will be recruited through flyers, WRNMMC intranet advertisements, internet advertisements, social media, email, newsletters, listservs, referrals from treatment providers, presentations, and by word of mouth. Flyers will be placed only at MTF clinics whose Service Chief or more senior leadership has provided approval. For the WRNMMC Adult Partial Hospitalization Program, the study team will conduct a monthly brief recruitment presentation directly to a cohort of patients with an independent ombudsman in attendance in accordance with military regulation. The study team will encourage recruitment of a representative sample of the military PTSD population by enrollment of study participants through communicating with referral sources.

Participants will be recruited from patients participating in care at WRNMMC, who are likely to meet eligibility criteria. Providers will refer potential and interested participants to the research study team after completion of their clinical visit by providing them with the IRB-approved flyer that contains the link to the Study Prescreening Form. Providers and investigators will clearly state that the study is for research purposes only, is completely voluntary, and is not being provided as clinical guidance or advice. All recruitment procedures will comply with WRNMMC Department of Research Programs HRPO Policy Memorandum 3.a and make clear that any proposed research protocols or research opportunities are separate from their clinical care.

Once a potential participant provides their contact information, a member of the research team will contact the individual via phone or email to gauge interest in participating in the study. The background of the study, study procedures, and potential risks and benefits of participation will be explained to each potential participant.

A recruitment flyer will be available for distribution by referring providers, USSOCOM Warrior Care Program representatives, and military/veteran-related nonprofit organization representatives that will detail the study's requirements, eligibility criteria, and point-of-contact. Similar

information will be available on the WRNMMC intranet. If a person expresses interest in participation, they will then be given the recruitment flyer with pertinent study details for their consideration and a QR code that links to the Prescreening Questionnaire. An intranet posting will also be made with the relevant and unformatted information from the recruitment flyer. All recruitment materials will be IRB-approved.

Eligibility for further screening will not be conducted until after the potential participant has completed the informed consent procedure. The informed consent procedure will take place in a private place either face-to-face or virtually using a Health Insurance Portability and Accountability Act (HIPAA)-compliant and DoD-approved video conferencing platform.

6 Study Intervention(s) and Concomitant Therapy

The study intervention is the combination of a course of psychotherapy integrating Acceptance and Commitment Therapy across three 90-minute Preparation Sessions, nine 90-minute Integration Sessions, and three 6-8 hour Dosing Sessions involving an initial dose of study drug (full-dose MDMA or low-dose MDMA) followed by an optional supplemental dose 2 hours (±15 minutes) later. See Figure 1 and Section 8.4 for a more detailed overview of the full intervention course.

6.1 Investigational Products

6.1.1 MDMA

The Active Pharmaceutical Ingredient (API) to be used in this protocol is MDMA (as hydrochloride salt). This ring-substituted phenethylamine has a complex pharmacology, but it acts most prominently as a monoamine releaser and reuptake inhibitor. Its direct actions on serotonergic, adrenergic, and other receptors are considerably lower. Refer to the Investigator's Brochure for a comprehensive review of the pharmacology, effects and proposed mechanisms of action of the IP. All drug is encapsulated in hydroxypropylmethylcellulose capsules.

Table 8. Study Medication Interventions Administered

	Active Intervention (Full-Dose MDMA HCl)	**Active Control Intervention (Low-dose MDMA HCl)**
Intervention description	MDMA as a hydrochloride salt (HCl). Initial dose for first Dosing Session includes 80 mg MDMA HCl followed 2 hours (± 15 minutes) later by a supplemental dose of 40 mg MDMA HCl. Initial doses for second and third Dosing Sessions include 80 mg MDMA HCl to 120 mg MDMA HCl followed 2 hours (± 15 minutes) later by a supplemental	MDMA as a hydrochloride salt (HCl). Initial dose for first active control Dosing Session includes 40 mg MDMA HCl plus 0 mg inactive placebo, followed 2 hours (± 15 minutes) later by the 0 mg supplemental inactive placebo. Initial doses for second and third active control Dosing Sessions include 40 mg MDMA HCl plus 0 mg inactive placebo, followed 2 hours (± 15

	Active Intervention (Full-Dose MDMA HCl)	**Active Control Intervention (Low-dose MDMA HCl)**
	dose of 40 mg MDMA HCl or 60 mg MDMA HCl.	minutes) later by the 0 mg supplemental inactive placebo.
Type	Drug (Capsule Dosage Form)	Drug (Capsule Dosage Form)
Dose Formulation	Hydroxypropylmethylcellulose capsule	Hydroxypropylmethylcellulose capsule
Unit Dose Strength(s)	40 mg or 60 mg MDMA HCl	40 mg MDMA HCl or 0 mg inactive placebo
Dosage Level(s)	Initial: 2 capsules of 40 mg MDMA HCl for first Dosing Session, 2 capsules of 60 mg MDMA HCl for second Dosing Session, and 2 capsules of either 40 mg or 60 mg MDMA HCl for third Dosing Session. Supplemental: one (1) capsule 40 mg MDMA HCl (if 80 mg total initial dose) or 60 mg capsule MDMA HCl (if 120 mg total initial dose).	Initial: 1 capsule 40 mg MDMA HCl plus 1 inactive placebo capsule for all three Dosing Sessions. Supplemental: 1 capsule inactive placebo
Inactive Ingredients	Mannitol USP and magnesium stearate NF	Mannitol USP and magnesium stearate NF
Route of Administration	Oral	Oral
Use	Experimental	Experimental
IP	IP	IP
Sourcing	Provided by Resilient Pharmaceuticals	Active control provided by Resilient Pharmaceuticals Inactive Placebo Provided by Resilient Pharmaceuticals
Packaging and Labeling	Each container will be labeled as required per country and federal, state, and local regulations. Each container will be labeled with the statement, Caution: New Drug – Limited by Federal (or United States) law to investigational use.	Each container will be labeled as required per country and federal, state, and local regulations. Each container will be labeled with the statement, “Caution: New Drug – Limited by Federal (or United States) law to investigational use.”

6.1.2 Product Packaging and Labeling

The IP for each Dosing Session will be packaged in one primary container, labeled with a unique container number, protocol number, blinded IP name, Dosing Session number, and a statement that the IP is restricted to clinical trial use only. The aforementioned statement, in compliance

with 21CFR312.6, will state “Caution: New Drug — Limited by Federal (or United States) law to investigational use.” All labels will comply with local, state, and federal regulations. The initial and supplemental dose will be labeled as such and packaged separately within the primary container. There will be one primary two containers per participant per Dosing Session: one will contain 2 capsules for the initial dose and the other will contain 1 capsule for the supplemental dose.

6.1.3 Storage

The study IP will be stored in the WRNMMC Investigational Pharmacy. MDMA is a Schedule I controlled substance and will be stored and handled in compliance with all relevant federal, state, and local regulations. In accordance with these requirements, the appropriate license holder or designee will be responsible for receiving, maintaining, dispensing, and administering the MDMA for approved uses only. The license holder is responsible for ensuring that the MDMA is stored securely in accordance with the requirements of all relevant local, national, and international regulatory authorities. 40 mg MDMA HCl and 60 mg MDMA HCl capsules currently have a shelf life of 48 months with recommended storage conditions at ambient temperatures between 20°C to 25°C, with excursions permitted from 15°C to 30°C.

6.1.4 Handling: Accountability and Administration

Forms will be created to track IP accountability and administration throughout the study. Blinded IP accountability and administration logs will be reviewed during routine monitoring visits or through central monitoring. MDMA will be handled in accordance with all local, state, federal, and military regulations and forms pertaining to the use of controlled substances, and forms will be maintained by the appropriate controlled substance license holder or designee. Each primary container label will contain a unique container number for the IP assigned to a single Dosing Session. The container numbers will be used to track IP administration in the Source Record and the IP administration log. The web-based randomization system will enable tracking of blinded primary containers for accountability purposes.

A pause/timeout will occur while both the study physician and a second study team member will verify that the number of capsules in hand aligns with the intended number of capsules to be dosed and will cross-reference that with the participant ID prior to administration. The study physician or a delegated study clinician will provide the IP to the participant to self-administer. Date and time of IP administration will be documented in the Source Record and the IP administration log.

6.2 Therapy

6.2.1 Description of Therapeutic Model

The therapeutic modality for this study will integrate principles of ACT that have been adapted for MDMA-AT. All therapy teams will be extensively trained in both ACT and MDMA-AT before the study to ensure all participants are treated in a similar manner. MDMA-AT is derived fundamentally from elements of a person-centered, process-oriented approach that endeavors to establish a dynamic of trust, respect, and supportive self-discovery. The integration of ACT will

add specific strategies therapists can utilize in each session to facilitate psychological flexibility and reduce pathological mechanisms associated with PTSD. MDMA-AT primarily consists of three distinct types of sessions: preparatory, MDMA dosing, and integration sessions. Preceding the first MDMA Dosing Session are three 90-minute Preparatory Sessions designed to educate the participant about the treatment, build a therapeutic alliance, facilitate present moment awareness, orient to session, prepare the participant to engage in acceptance during the Dosing Session, utilize cognitive defusion, reinforce self-as-context, and clarify participant values and therapeutic goals. The Preparatory Sessions are utilized to gather participant history, establishing an effective therapeutic alliance, and to introduce therapy concepts. It provides an important opportunity for the therapists to address the participant's questions and concerns, as well as to prepare the participant for MDMA-assisted sessions by familiarizing them with the logistics of the sessions and the therapeutic approach that will be used. This preparation should be done with the intention of helping the participant feel a sense of openness and safety in the therapeutic setting.

Concomitant to the enrollment/baseline period participants will complete three 90 minute preparatory therapy sessions. The primary purposes of the preparatory sessions are to educate the participant about the treatment, build a therapeutic alliance, and establish the participants therapeutic aim – or what is more commonly known in psychedelic medicine as setting one's intent. Using ACT as the therapeutic frame, the therapist will maintain an active case conceptualization throughout treatment using the psychological flexibility model in which ACT is based. One of the primary goals of the preparatory sessions are to help patients align the intention in accordance with personal values. Establishing therapeutic intent is what in part differentiates MDMA-AT from taking MDMA in non-clinical settings where one's intent may be recreation. The therapist endeavors to establish and maintain a dynamic that the participant is truly the expert of their own experience and thus should be entrusted with determining the direction of the therapy. In contrast to recreational use of MDMA which is often externally-focused and enjoyable, the experience of MDMA-AT tends to be more emotionally challenging and described by the patient as therapeutic "work." The therapeutic approach, ACT, is derived from elements of traditional cognitive behavioral therapy and is a person-centered, process-oriented approach that endeavors to establish a process of trust and respect.

The medication-assisted sessions consist of 3 Dosing Sessions, each approximately 1 month apart. The entire Dosing Session is anticipated to take 6-8 hours. During the Dosing Sessions, therapists will help participants implement cognitive defusion techniques regarding their thoughts, sensations, imagery, and memories as appropriate. Additionally, therapists will help participants practice present moment awareness, acceptance, cognitive defusion, self-as-context, values awareness, and connecting committed action with their MDMA-dosing experiences. The therapist will be present the entire day and will be remotely monitored by a supervisory member of the research team through a secure HIPAA-compliant, DoD-approved live audio/video system. The therapist and participant will discuss goals for the session and self-administration of medication will commence. In most cases, participants maintain an inner-directed experience for the majority of the session while the therapist actively attends to the participant's needs as they arise. In some cases, the participant may have an entirely inward experience where the therapist may only converse with the patient in several sentences total throughout the 6-8 hour session. In other cases, a participant may prefer to have an externally-directed experience for most of the session, requiring more active engagement with the therapist. Regardless, the role of the therapist

is to occasionally encourage the participant towards an inner-directed experience while also being supportive of any externally-directed experiences that are within the participant's therapeutic intent. Here, the ACT treatment processes will similarly be used to help guide these sessions. Further, the therapist will use their observations during medicine sessions to update their ACT case conceptualization, which will help guide integration sessions.

Each MDMA Dosing Session for full-dose and low-dose MDMA groups is followed by three 90-minute Integration Sessions for a total of 9 Integration Sessions per course of treatment. The first of each trio of Integration Sessions occurs the morning after the Dosing Session. The 2nd Integration Session occurs within 3-14 days of the Dosing Session and the 3rd Integration Sessions occurs within 1 month of the Dosing Session. All Integration Sessions must be completed prior to the next Dosing Session. During the Integration Sessions, the therapists are present to answer any questions the participant may have, as well as to offer support and encouragement as the participant processes the emotional responses and new perceptions resulting from the MDMA-assisted session. The therapists take a supportive stance toward the participant's experiences while implementing the use of present moment awareness, acceptance, cognitive defusion, self-as-context, exploration of values, and reminding of committed action to facilitate learning from MDMA-assisted sessions. The primary emphases of the integration sessions are to 1) attend to the potential changes that were catalyzed, 2) expand upon them through person-centered exploration, and 3) explore how to integrate these changes into daily life by refining one's personal values, if necessary, assessing changes in the perspective of thoughts, emotions, and body sensations that leads to avoidance, and assigned home practices designed to meet the intentions established at the outset of treatment. New experiential knowledge, insights, and emotional shifts may have been catalyzed both during and after the most recent MDMA session. During the Integration Sessions, the participant is invited to share details of their MDMA or active control experience, though this is not required.

6.2.2 Acceptance and Commitment Therapy Description (ACT)

Acceptance and Commitment Therapy (ACT) is a therapy that utilizes contextual behavioral science and functional contextualism to improve psychological flexibility through acceptance, cognitive defusion, mindfully attending to the present moment, self-as-context, values, and committed action.[186] Primarily, ACT targets experiential avoidance (i.e., an unwillingness to experience events and attempts to escape/avoid) which results in the reinforcement of generalized avoidance which is an important factor in PTSD.[187] PTSD often results in avoidance of environmental stimuli, memories, thoughts, and reminders associated with the trauma.[187] ACT can help reduce the avoidance that perpetuates intrusive thoughts, nightmares, hyperarousal, and distress in PTSD.[187] ACT has been found to be an effective therapy for several mental health diagnoses, including PTSD.[188]

6.2.3 Therapy Training Program

Study therapists will be trained by an accepted MDMA Therapy Training Program or equivalent and will also undergo additional training specific to integrating ACT principles as a therapeutic framework.

The MDMA Therapy Training Program is designed to teach competency in applying the essential elements of MDMA-AT. Therapy team members will receive specific training in the MDMA-AT modality, protocol, and the latest version of the Investigator's Brochure (IB). Training in the therapy method consists of reading the Treatment Manual, completing online training modules, and participating in in-person or online training that includes watching and discussing videos of Dosing/Preparation/Integration Sessions. The final part of training includes Training Consultation from a trained and qualified independent contractor working as a Training Consultant. For any therapy team members who did not receive consultation through prior work, Training Consultation is required (and associated costs will be covered by the grant funding supporting this study). A Training Consultation Plan will be developed and shared with the treatment teams. The required elements of the therapy are defined in the study Treatment Manual. In addition to this specific training, it is required that participating therapy team members have the proper background, education, and experience.

For clinicians actively undergoing Training Consultation, all therapy sessions (including MDMA-assisted and non-drug sessions) will need to be video and audio-recorded and made accessible to the independently contracted Training Consultant.

In addition to the MDMA Therapy training program, all therapists will also undergo specific training on how to integrate ACT principles during Preparatory, Dosing, and Integration Sessions to help maximize therapeutic benefit. This includes teaching mindfulness exercises to increase present moment awareness and grounding techniques and discussing the importance of having an open and inquiring attitude during Dosing Sessions. This may be challenging for individuals with PTSD, as fear of losing emotional control is a common feature of PTSD. There also may be an inclination to control the dosing experience (e.g., desiring a more intense or less intense subjective experience, wanting the experience to end or be elongated, etc.). Thus, the therapist will be instructed to explore any control agenda(s) their patient may have prior to the Dosing Sessions. ACT specific methods, such as the "tug of war" exercise, will be used to teach the crucial skill of allowing experiences to be as they are versus attempts to control. All therapists will be certified to deliver this form of therapy. A final baseline screening completion and eligibility check will be completed prior to Dosing Session.

6.2.4 Therapy Team Qualifications

See Section 6.3.1 for definitions of *Clinician*, *Therapist*, and various categories of *Monitors*.

Study *Clinicians* or *Therapists* who may engage with participants during therapy or dosing sessions must meet the following minimum requirements:

- Licensed to practice psychotherapy independently according to state and local requirements. Examples of acceptable professional credentials or degree programs include:
    - Clinical or counseling psychologist (PhD or PsyD)
    - Psychiatrist or other physician (MD or DO)
    - Licensed Clinical Social Worker (LCSW)
    - Licensed Marriage and Family Therapist (LMFT)
    - Licensed Clinical Professional Counselor (LCPC)
    - Licensed Mental Health Counselors (LMHC)

  - Psychiatric Nurse Practitioner (Psychiatric NP or PMHNP)
  - Physicians Assistant (PA) with focused experience in psychiatric care
- Have at least one year of experience in a mental healthcare setting.
- Complete training in an accepted MDMA-Assisted Therapy training program.
- Complete training in the study-specific MDMA-ACT training program.
- Complete protocol-specific training, including clinically-relevant standard operating procedures
- Complete Prevention and Management of Disruptive Behavior-Military (PMDB-M) training
- Have current Basic Life Support (BLS) certification

Clinical Assistant Monitors (See Section 6.3.1 for definition) must meet the following requirements:

- Meets the definitions of both Assistant Monitor and Clinical Assistant Monitor per Section 6.3.1.
- Credentialed to provide clinical care according to state and local requirements, or are on track to obtain licensure through an advanced degree program or post-graduate professional experience. Examples of acceptable professional credentials or degree programs include but are not limited to:
  - Registered Nurse (RN)
  - Licensed Practical Nurse (LPN)
  - Mental Health Technician (MHT)
  - Paramedic
- Have at least one year of experience in a licensed mental healthcare setting.
- Complete training in an accepted MDMA-Assisted Therapy training program.
- Complete protocol-specific training, including clinically-relevant standard operating procedures
- Complete Prevention and Management of Disruptive Behavior-Military (PMDB-M) training
- Have current Basic Life Support (BLS) certification

Non-clinical Assistant Monitors must meet the following requirements:

- Meets the definitions of both Assistant Monitor and Non-clinical Assistant Monitor per Section 6.3.1.
- Complete non-clinical portions (asynchronous and didactic portions but not portions that involve working with a participant) of an accepted MDMA-Assisted Therapy training program.
- Complete protocol-specific training, including all relevant standard operating procedures
- Complete Prevention and Management of Disruptive Behavior-Military (PMDB-M) training
- Have current Basic Life Support (BLS) certification

The study therapy team must meet the following minimum requirements:

- The site must have at least one person licensed to manage and administer controlled substances.

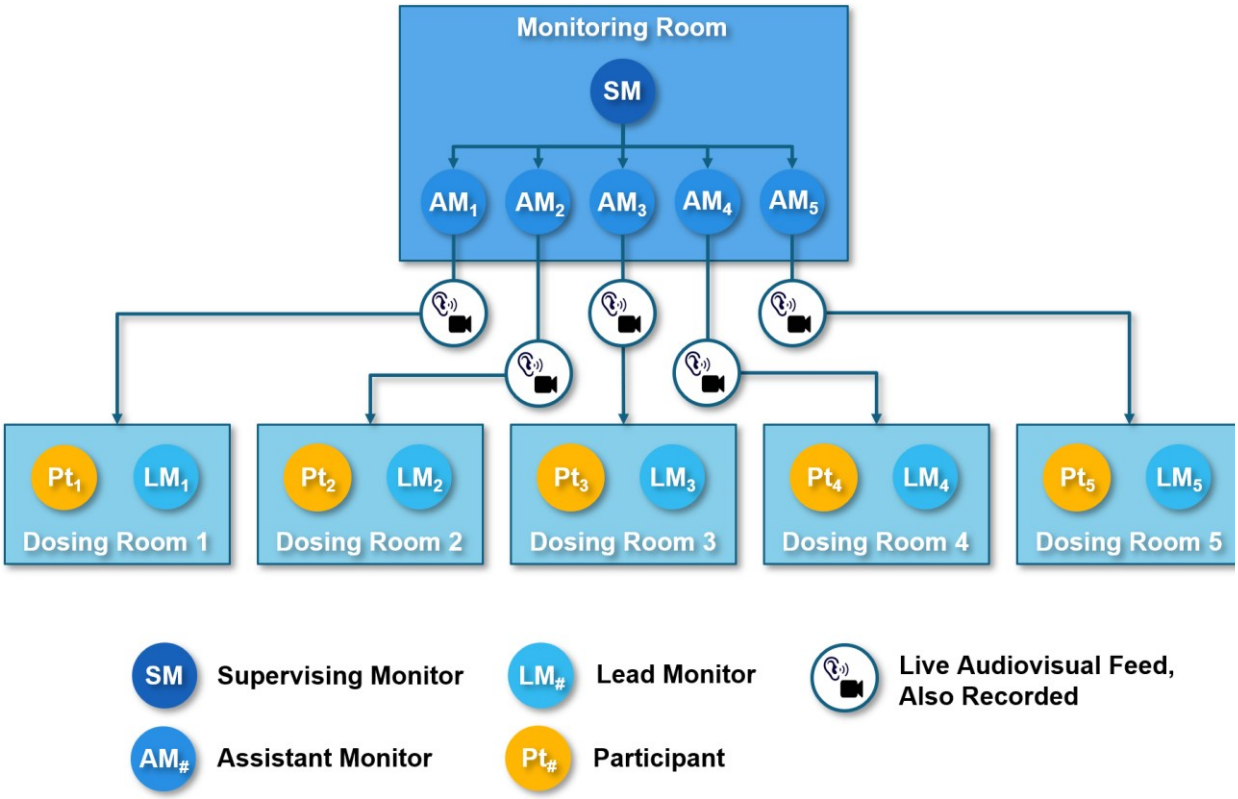
- A licensed independent medical provider (physician, NP, or PA) will be on the study team to assess participant safety. During Dosing Sessions, this medical provider will be on the premises and able to reach the dosing rooms within 5 minutes in the event of a medical or psychiatric emergency.

6.3 Simultaneous Dosing Model

Previous MDMA-AT clinical trials have relied on a two-therapist model, with both therapists present for all Preparation, Dosing, and Integration Sessions. While effective, this approach is highly resource-intensive and may limit accessibility and scalability. To evaluate a more efficient and scalable approach for real-world settings, this study will implement a Simultaneous Dosing Model. In this model, one therapist (Lead Monitor) is present in each dosing room with a participant, and up to five Dosing Sessions may occur simultaneously in five different rooms. A Supervising Monitor (a clinician) and other Assistant Monitors (can be either clinical or non-clinical study team members) will monitor all sessions in real-time from a nearby control room via a live audio-video feed. If a therapist signals the need for assistance, the Supervising Monitor or an authorized Assistant Monitor will immediately respond and provide support. The therapist will be relieved for breaks by an Assistant Monitor to ensure participants are never left alone during Dosing Sessions.

This Simultaneous Dosing Model has been previously used in FDA IND-regulated psilocybin therapy trials for depression, with protocols approved by IRBs such as Advarra and the Sheppard Pratt Health System.[178,179] These studies did not identify any new safety signals compared to traditional models. Another psilocybin study in Europe that concurrently dosed up to six healthy volunteers also reported no serious treatment-emergent adverse events.[180] Although our trial will be the first to apply this model to MDMA-AT, our team has visited and consulted with both U.S. psychedelic research centers that pioneered this model to incorporate best practices.

Figure 3. Simultaneous Dosing Model



Note: Every effort will be made to prioritize assigning only 1 Dosing Room to be monitored by each available Assistant Monitor. When the number of active Dosing Rooms exceeds the number of available Assistant Monitors (e.g., an Assistant Monitor is assisting with another task or is otherwise unavailable): 1) Assistant Monitors may monitor up to 2 Dosing Rooms, and 2) the Supervising Monitor may fulfill the role of the Assistant Monitor in addition to their role as Supervising Monitor. Each Dosing Room will *always* be monitored by an Assistant Monitor, Supervising Monitor, or both.

6.3.1 Definitions, Roles, and Responsibilities for the Simultaneous Dosing Model

The following are definitions of roles and responsibilities related to the Simultaneous Dosing Model:

- Clinician or Therapist
  - A *Clinician* or *Therapist* in the context of this study is defined as a healthcare provider with graduate-level professional training who is independently licensed to provide psychotherapy to treat mental health conditions. *Clinicians* or *Therapists* may be physicians (MD/DO), nurse practitioners (NP/PMHNP), physician's assistants (PA), clinical psychologist (PhD/PsyD), licensed clinical social workers (LCSW), licensed marriage and family therapist (LMFT), licensed mental health counselors (LMHC), licensed clinical professional counselors (LCPC), etc.

- Lead Monitor
    - The *Lead Monitor* is the primary clinician assigned to work with a specific participant by providing psychotherapeutic support according to the Treatment Manual during all preparation, dosing, and integration sessions. Another study clinician may temporarily act as a participant's Lead Monitor when the assigned Lead Monitor is unavailable for a portion or entirety of a particular preparation, dosing, or integration session.
- Supervising Monitor
    - The *Supervising Monitor* is a *Clinical Assistant Monitor* who is the head independently-licensed clinician responsible for overseeing the live audiovisual monitoring of *all* simultaneous dosing rooms. The Supervising Monitor determines how to initially respond to each Support Event, and if needed, authorizes the appropriate Assistant Monitor to respond to a given Support Event.
    - If the Supervising Monitor is a therapist and not an independently licensed medical provider (physician, nurse practitioner, or physician's assistant), one medical provider must be immediately available to respond to the dosing rooms in-person within 5 minutes (FDA draft guidance for psychedelic clinical trials recommends within 15 minutes;[189] although this protocol states a response time of within 5 minutes, we anticipate a response time of within seconds in our study due to at least one if not multiple medical providers on the study team always being immediately available during Dosing Sessions).
- Assistant Monitor
    - An *Assistant Monitor* is a qualified study team member who is able to respond to or assist with a Support Event. There will always be either an Assistant Monitor or Supervising Monitor actively monitoring the live audiovisual feed for each dosing room.
    - Assistant Monitors may either be a clinician ("*Clinical Assistant Monitor*") or a non-clinician ("*Non-clinical Assistant Monitor*").
- Clinical Assistant Monitor
    - A *Clinical Assistant Monitor* is an Assistant Monitor who is a clinical professional with appropriate training to provide clinical care under their license or another clinical professional's license. Examples include but are not limited to clinicians, therapists, nurses [registered nurses (RNs), licensed practical nurses (LPNs), or similar], or mental health technicians.
- Non-clinical Assistant Monitor
    - A *Non-clinical Assistant Monitor* is an Assistant Monitor who does not meet the criteria of Clinical Assistant Monitor. Examples include study coordinator or research assistant.

6.3.2 Roles and Responsibilities for Study

A list of study personnel will be maintained by the PI or designee. The list must be available for review by clinical study monitors and representatives of the sponsor (Defense Health Agency Research & Development - Medical Research & Development Command [DHA R&D - MRDC] Office of Regulated Activities [ORA]). Study roles and responsibilities are described in

Appendix D, with additional descriptions of roles specific to the Simultaneous Dosing Model detailed in Section 6.3.1.

6.3.3 Support Events

Support Events during Dosing Sessions will be categorized into one of six risk categories. These categories are Emergent, Urgent, or Routine *Participant* events and Emergent, Urgent, or Routine *Therapist* events.

1. **Emergent (High Risk)**
    a. Participant
        i. *Emergent-Participant* events are defined as events that would be reasonable to anticipate could lead to lasting negative medical or psychiatric impact for the participant without immediate appropriate intervention or additional support. These events still require immediate assistance from a Supervising or Assistant Monitor with the appropriate clinical training to manage the acute problem, even when the Lead Monitor in the room is appropriately trained for the acute problem and appears to be managing the event appropriately.
        ii. E.g., the participant appears to be having an acute medical event that could lead to morbidity or mortality without immediate intervention (e.g., acute chest pain, loss of consciousness, stroke-like symptoms, or seizure-like symptoms), or the participant appears to be at acute risk of harm to themselves or others (e.g., exhibiting threats of harm self/others or acute suicidal/threatening behaviors).
    b. Therapist
        i. *Emergent-Therapist* events are defined as events that would be reasonable to anticipate could lead to lasting negative medical or psychiatric impact for the therapist without immediate appropriate intervention or additional support.
        ii. E.g., the therapist appears to be having an acute medical event, appears to be at acute risk of harm to themselves or others, or is exhibiting unusual behavior.
2. **Urgent (Moderate Risk)**
    a. Participant
        i. *Urgent-Participant* events are defined as events where the participant is exposed to an increased clinical risk that still requires additional clinical support or evaluation that is beyond the capabilities of the Lead Monitor to manage on their own, but the event does not meet the severity of Emergent-Participant criteria.
        ii. E.g., the participant is experiencing visible or audible distress that is unmanageable by the Lead Monitor alone, or the participant is experiencing an AE such as severe nausea or severe anxiety that requires further assessment and/or intervention that is beyond the clinical scope of the Lead Monitor alone.
    b. Therapist

i. *Urgent-Therapist* events are defined as events where the therapist is exposed to an increased risk of being unable to fully attend to their clinical responsibilities on their own, requiring additional support to do so, but the event does not meet the severity of Emergent-Therapist criteria.
ii. E.g., the therapist appears to be overwhelmed, distressed, confused, or disoriented; the therapist appears to be experiencing early signs of an illness, such as nausea or dizziness; or the therapist appears to fall asleep.

3. Routine (Low Risk)

a. Participant
   i. *Routine-Participant* events are defined as routinely anticipated low-risk events that neither compromise participant safety nor require therapeutic intervention, yet involve an Assistant Monitor to provide temporary assistance to the participant. These types of events are anticipated to occur potentially during every Dosing Session, do not require specialized clinical training, and may be addressed by a study team member who is either a Clinical or Non-clinical Assistant Monitor.
   ii. E.g., the participant needs an Assistant Monitor to escort them to the bathroom, to provide snacks or a drink that is not already in the room, or to provide an extra pillow or blanket.

b. Therapist
   i. *Routine-Therapist* events are defined as routinely anticipated low-risk events that do not compromise participant safety or therapeutic continuity, yet require an Assistant Monitor to provide temporary assistance to the Lead Monitor. These events are anticipated to occur potentially during every Dosing Session, do not require specialized clinical training, and may be addressed by a study team member who is either a Clinical or Non-Clinical Assistant Monitor.
   ii. E.g., an Assistant Monitor temporarily sits in the dosing room while the Lead Monitor is on their lunch break or in the restroom.

Additional procedures to further enhance safety:

1. Depending on the level of support required, the Supervising Monitor may determine whether to go into the room themselves, delegate to another qualified study team member, or activate a Code Blue (medical emergencies) or Code Gray (combative or violent person) response in accordance with WRNMMC administrative instruction (Supplement 1 and 2, respectively).
2. If a Support Event requires more specialized training or intervention than can be provided the available study medical provider, any study team member is permitted to directly initiate a Code Blue (Supplement 1) or Code Gray (Supplement 2).
3. If the evaluating study medical provider deems that the participant requires acute medical evaluation that is beyond the provider's scope or capabilities but does not require emergent evaluation and intervention, another option is for the provider to call ahead to the WRNMMC Emergency Department to provide them with any relevant details about the participant's history and physical while the participant is being transported directly to the Emergency Department for further evaluation.

4. All study team members will receive training on Code Blue and Code Gray activation. Additionally, all study team members will complete Prevention and Management of Disruptive Behavior-Military (PMDB-M) training.
5. There may be low-risk scenarios not triggered by a clinical event in which the presence of or intervention by another study team member, in addition to the Lead Monitor, is permitted. Examples include the planned presence of an additional study team member for training, quality assurance, and/or study fidelity. The planned presence of an additional study team member in these scenarios should not be recorded as a Support Event; however, a separate Monitor who is not initially in the dosing room who responds to provide in-room support should still be recorded as a Support Event per protocol.
6. Although overlapping Support Events across different dosing rooms is inevitable and expected, the study team will attempt to schedule Routine Support Events in a manner that minimizes overlap with other Support Events, while not compromising the safety of participants and clinicians. This is to optimize the availability of Assistant Monitors in case of an Urgent or Emergent Support Event.
    a. For example, if one room is undergoing an Urgent or Emergent Support Event, responding to a Routine Support Event request will be deprioritized and may be delayed until it is appropriate to respond in the context of the time-sensitivity of the Routine Support Event balanced against the needs of other ongoing Support Events.
    b. Another example is a scenario where there are four simultaneous Routine Support Events anticipated for therapist lunch breaks. The team would not strictly prioritize maximizing therapist convenience without consideration for participant safety by scheduling all lunch breaks at the therapists' preferred times which could entirely overlap, for example from 12:00-13:00. This would minimize the availability of Assistant Monitors during that time and compromise participant safety. On the other hand, the team would also not strictly minimize overlap of Routine Support Events without consideration for maintaining sensitivity to therapists' needs as well; this could equate to scheduling all lunch breaks strictly in sequence without any overlap and thus delaying some lunch break much later into the afternoon which could compromise therapist safety. Instead, an example of a solution to the four lunch breaks scenario would be to schedule the lunch breaks at 11:00-12:00, 11:30-12:30, 12:00-13:00, and 12:30-13:30. Ultimately, the driving philosophy in coordinating Routine Support Events is to optimize for minimizing overlap of these Routine Support Events while still balancing against maintaining sensitivity to the needs of the therapists in manner that does not compromise safety for either participants or therapists.
7. All Support Event data collection will be reviewed with the study team before the next scheduled Dosing Session. Corrective and preventive action plans, as well as additional policies and procedures, will be implemented as warranted.

6.3.4 Non-Clinical Assistant Monitors Covering Routine Support Events

Non-clinical Assistant Monitors may provide temporary in-room monitoring coverage during a Dosing Session when the Supervising Monitor determines that the scenario constitutes a low-risk Routine Support Event (e.g., the Lead Monitor temporarily steps away for a restroom or lunch break). This coverage is only permitted when the participant is lying comfortably, is in no

distress, does not require therapeutic interaction, and only requires basic observation or non-therapeutic assistance.

Temporary in-room monitoring coverage by a Non-clinical Assistant Monitor is limited to:

- *One 60-minute episode* per participant per Dosing Session (e.g., Lead Monitor's lunch break).
- *Up to three 10-minute episodes* per participant per Dosing Session (e.g., Lead Monitor's restroom breaks). Additional brief episodes of coverage are permitted in unanticipated extenuating circumstances (e.g., Lead Monitor requires more than three breaks to pump, use the restroom, address a routine/anticipated/low-risk personal medical matter, etc.).

Permitted actions by Non-clinical Assistant Monitors during Routine Support Events include the following:

- Providing basic non-therapeutic assistance.
    - E.g., providing bottled hydration, snacks, pillows, or blankets, or escorting the participant to the restroom)
- Answering basic non-therapeutic questions.
    - E.g., "Where did the therapist go?" "Can you get me some water?" "Can you get me a snack?" "Can you help me to the bathroom?" etc.
- Informing the participant why the Non-clinical Assistant Monitor is currently in the room, why the Lead Monitor is currently not in the room, approximately when the Lead Monitor will return, what the Non-clinical Assistant Monitor can assist with, and what kinds of needs requests or questions will require notification of a study clinician to assist with.
    - E.g., "Hi, I'll be here while your therapist is out for lunch. She should return in about 30-60 minutes. If you have any basic requests or non-clinical questions, I can help you with that. If you have any clinically-related questions or needs, please let me know so I can notify a clinician."
- Taking notes regarding any non-urgent verbalizations or therapeutic processes that occur. These notes will be provided to the therapist upon their return to the room for the therapist to attend to based on their clinical judgment.
    - E.g., a participant with their eyemask and headphones still on may speak out loud in a non-distressed manner, while not requesting therapeutic support; the Non-clinical Assistant Monitor will communicate what the participant said or did to the Lead Monitor upon their return to the room.
- If the participant is not in distress, is not expressing other needs, and is engaging with their external environment (e.g., does not have their eyemask and/or headphones on), the Non-clinical Assistant Monitor may offer a gentle reminder, if applicable, to put their eyemask and/or headphones back on and to return their attention to their inner experience.

Prohibited actions by Non-clinical Assistant Monitors during Routine Support Events include the following:

- Providing psychotherapy or therapeutic touch
- Administering any clinical intervention

- Responding to clinical questions (e.g., “My heart is racing. Is that normal?” “When can I drive?” “Do you think I got a low dose?” etc.)

6.3.5 Data Elements for Simultaneous Dosing Model

The study will collect the following data on Support Event reporting forms for each participant for each Dosing Session to evaluate the safety and feasibility of the Simultaneous Dosing Model to inform future studies and potential clinical implementation:

- Nature of Support Events that trigger the need for a Supervising or Assistant Monitor to enter a dosing room.
    - Support Events will be categorized as Emergent-, Urgent-, or Routine-Participant events or Emergent-, Urgent-, or Routine-Therapist events.
- Time that the Support Event request was either made by the Lead Monitor or a need was recognized by the Supervising Monitor for a study team member to enter a dosing room. Support Events that were scheduled ahead of time prior to the start of the Dosing Session (e.g., scheduling a break for lunch or pumping ahead of time) will be annotated as having been scheduled prior to start of the Dosing Session and will not have a request/recognition time associated with it.
- Time the supporting Monitor (Lead, Supervising, or Assistant Monitor) enters and leaves the room for a Support Event (response time as well as duration of event).
- Interventions completed by the supporting Monitor during a Support Event.
- Which study team member enters the room to respond to a Support Event.
- All levels of training that could have appropriately addressed each Support Event, e.g., non-clinical study staff, mental health technician, nurse, therapist, medical provider, etc.
- Identification of any potential barriers for the appropriate Monitor to have responded sooner. There will be separate areas on the Support Event Reporting Form for the Supervising Monitor, Assistant Monitor, and “Other” study team member to each have an opportunity to either provide a free-text response and/or select “None.”
- Other safety, process, and quality measures as needed.

The Supervising Monitor or delegated study team member will be responsible for ensuring the Support Event reporting form is completed for all participants for each Dosing Session.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Study Randomization

Participants who have been determined at screening to be eligible for enrollment, have provided full written informed consent, and are not assigned to the open-label cohort at enrollment, will be randomized after the last Preparation Session but before the 1st Dosing Session 1:1 to the full-dose MDMA-AT group or the low-dose MDMA-AT group. Randomization will be managed via REDCap based on a centralized randomization sequence developed by the independent DCAC to maintain blinding. The sequence will randomize participants within blocks and without stratification.

6.4.2 Study Blinding

Study participants, study personnel, investigators, Independent Safety Monitor, and the study sponsor will be blinded to treatment assignment until the last participant has completed all scheduled visits, the database has been cleaned, and the clinical database locked. Exceptions to blinding procedures will be made on an individual participant basis in the event of an unexpected medical event when it is determined by the PI or Independent Safety Monitor that knowledge of the study arm assignment or dose received could mitigate health risk (see Section 6.4.3 Study Unblinding).

The only study personnel that will remain unblinded will be the Investigational Pharmacist, unblinded Clinical Monitor, and independent Data Coordinating and Analysis Center (DCAC) personnel (one statistician, one programmer, the project oversight manager, data manager, and the Associate Director). All analyses conducted prior to the completion of the study will be performed by the unblinded statistician, and results will only be presented in aggregate to protect the participant-level blind, as described in Section 9.14 Statistical Analyses.

6.4.3 Study Unblinding

Blinding of study personnel, participants and the sponsor will be maintained until the last participant has completed all scheduled visits, the database has been cleaned, and the clinical database locked, upon which participants will be notified of their study arm assignment.

The PI has the authority to unblind a participant's treatment if identification of the study treatment is required for treatment during a medical emergency. The PI should consult with the Independent Safety Monitor and the pharmacovigilance physician in the DHA R&D - MRDC ORA before unblinding if the event is not a medical emergency. If unblinding is justified, the PI will follow the study-specific unblinding procedures outlined in this section. The pharmacovigilance physician can provide guidance in the unblinding process if requested but is not responsible for the actual task of unblinding. The date and reason that the blind was broken will be recorded in the source documentation and CRFs, as applicable and the sponsor will be notified within 24 hours after breaking the blind. Study personnel will record the unblinding as a protocol deviation and report the deviation to the site IRB.

For cases of non-emergency unblinding, the sponsor's representative in consultation with the DHA R&D - MRDC ORA Product Safety Surveillance Office (PSSO) will make the final determination of whether to approve the unblinding request. If approved by DHA R&D - MRDC ORA PSSO, the Principal Investigator will request the unblinding of the participant's assignment from the unblinded statistical team. The DHA R&D - MRDC ORA PSSO can guide the unblinding process if requested but is not responsible for the actual task of unblinding.

Instances of unblinding that occur during the clinical portion of the study will be reported to the IRB and ORA after the unblinding occurs. If the unblinding is due to a death, related SAE or other immediately reportable event, the reportable event notification to the IRB and ORA will note the unblinding and a separate unblinding-specific notification will not be sent.

All participants who were randomized will be informed about the arm to which they were assigned after the last participant has completed all scheduled visits, the database has been cleaned, and the clinical database locked.

6.4.4 Independent Raters

To minimize bias in efficacy assessments, the study's primary outcome assessments will be performed at baseline, primary endpoint, and secondary endpoint by an independent pool of remote blinded and trained central raters who will have no interactions with participants or study personnel other than conducting the assessments remotely. Each CAPS-5-R assessment will be assigned a primary assessor and a double scorer, with assessments either live- or video-double scored depending on availability. Any score discrepancies are reviewed in group supervision with a qualified licensed clinical psychologist to reach consensus. Participants will be instructed to withhold their opinion on treatment group assignment from the raters. CAPS-5-R assessment data will be entered into the study REDCap database directly by the independent blinded assessment team. More information about the use of independent raters to conduct CAPS-5-R assessments can be found in Section 9.1.1.

6.5 Access to Study Intervention after the End of the Study

All participants will be informed that we are actively planning and working towards multiple avenues to potentially access full-dose MDMA-AT which we intend to offer all participants who are assigned to active control, complete the study, meet criteria, and are in good standing with the clinical site, regardless of the severity of their PTSD and comorbid symptoms. These avenues include: 1) a yet unfunded open-label MDMA-AT study, 2) yet-unsupported clinical implementation via Expanded Access or post-FDA-approval treatment, and 3) referral to other similar studies near their location. Participants will be informed that they will take priority for any avenues that are within the purview of our program at WRNMMC.

6.6 Treatment of Dosing Errors

Any dose of full-dose MDMA or low-dose MDMA that deviates from the intended dose should be documented as a dosing error as soon as it is discovered. Dosing errors will be documented in the electronic case report form (eCRF) and the deviation log. Dosing errors will be reported to the IRB, DSMB, Independent Safety Monitor, Investigational Pharmacy, ORA, and drug manufacturer in accordance with each respective entity's reporting requirements.

6.7 Concomitant Medications

Participants are permitted to continue medical, psychiatric, or psychotherapeutic interventions unless stated otherwise in this section or elsewhere in the protocol. Psychiatric medications requiring tapering prior to Dosing Sessions are addressed in Section 6.7.1; birth control considerations in Section 6.7.2; medications permitted during the study in Section 6.7.3; prohibited medications in Section 6.7.4; and washout parameters and tapering procedures in Section 6.7.5. The study team will evaluate concomitant medications for safety and eligibility at screening and at each subsequent visit throughout the study (Table 3 and Table 4).

6.7.1 Psychiatric Medications

A study medical provider (MD, DO, NP, or PA) will review concomitant medications during Screening. If the prospective participant is being treated with prohibited psychiatric medications

at enrollment, the prospective participant will be encouraged to discuss medication tapering with their outside prescribing clinician, if any, and will be required to give a study medical clinician permission to do so as well.

The study medical provider will consult the prescribing provider to initiate medication tapering for participants, as they must refrain from taking psychiatric medications throughout the study, with some exceptions (see Section 6.7.3 Permitted Concomitant Medications). The prescribing provider's opinion about medication discontinuation will be documented either in writing from the prescribing provider, or in writing by the study medical provider documenting phone contact with the prescribing provider. Tapering will follow a time course appropriate for the medication based on its half-life, with the Baseline CAPS-5-R scheduled to occur after complete washout for psychoactive medications and Dosing Session 1 scheduled to occur after complete washout for medications with drug-drug interactions with a psychiatric concern, which would be five half-lives plus at least 1 week for stabilization (5 half-lives for medications without psychiatric concerns.)

The therapist will request information about any changes in medication at each contact (see Table 3 and Table 4). A study medical provider will be responsible for reviewing and confirming all medications collected during the study. All medications, non-prescription and prescription, will be collected at Screening as well as all Preparation Sessions, Dosing Sessions, Integration Sessions, Primary Endpoint Visit, Follow-up Phase safety calls, and Secondary Endpoint Visit. Throughout the protocol, all medication changes including dosing changes, discontinuations, or additions to medications will be collected. The study team will also inquire about concomitant medication adherence and document all information on the Concomitant Medications case report form (CRF).

6.7.2 Birth Control Medications

Participants may discontinue birth control after the Primary Endpoint visit (1°), if necessary, and may continue taking medications after completing study enrollment after the final Secondary Endpoint visit (2°).

6.7.3 Permitted Concomitant Medications

A study medical provider may prescribe necessary and appropriate medications in accordance with local and state regulations during the study to treat AEs that do not respond to other management outlined in the Treatment Manual. Examples include concomitant benzodiazepines for uncontrolled anxiety (e.g., lorazepam at modest doses) or sleep aids (excluding trazodone) in compliance with Section 6.7.4 Prohibited Medications.

Any medications prescribed to manage an adverse effect (e.g., lorazepam for anxiety or zolpidem for insomnia) will not be considered a study intervention and will instead be documented on the Concomitant Medications eCRF. The route, frequency, and dose should be determined by the prescribing physician as clinically indicated. If these medications are stocked on site, they should be stored according to applicable national and local regulations.

Gabapentin or certain opioids (hydrocodone, morphine, and codeine) will be allowed when prescribed for pain management.

All psychoactive medications, herbal supplements, nonprescription medications, and prescription medications must be reviewed by the study team at least 2 weeks prior to each Dosing Session. Failure to comply with protocol requirements for concomitant medications may result in delay of the next Dosing Session or withdrawal from the study, depending on the clinical judgment of the PI and Independent Safety Monitor.

6.7.4 Prohibited Medications

Participants should refrain from use of any medications not approved by the study team from Baseline through Secondary Endpoint.

In consultation between the prescribing provider and the study medical provider, participants may be permitted to remain on their chronic daily dosing and regimen of permitted opioids to prevent intolerable pain flare ups and withdrawal symptoms if it is determined to be the safest treatment plan. However, participants on permitted opioids will be asked to avoid taking the opioid on days of Dosing Sessions, if it is determined to be safe to do so.

Participants should refrain from taking any prescription medications preceding each Dosing Session unless the research team has approved the medication.

The research team should only approve medications that clearly would not be expected to have any interactions with MDMA, including, but not limited to, any drugs with sympathomimetic activity (such as stimulants) or activity on the serotonin or other monoamine systems, and any other drugs that would be contraindicated with or have any interaction with monoamine oxidase inhibitors (MAOIs). Further guidance is provided in the Investigator's Brochure.

The following medications or substances may pose a safety risk or present potential confounds for interpretation of the data collected from this study as they have notable serotonergic effects, and thus, they should be prohibited from Baseline through Primary Endpoint:

- Cannabis, St. John's Wort, and other herbs and medicines with notable serotonergic effects
- Diphenhydramine, unless prior approval is granted by the study clinician
- Selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or other antidepressant; if used between the first Dosing Session and Primary Endpoint, the participant will be permitted to finish the current intervention cycle, will be withdrawn from future intervention cycles, and will continue with all Primary/Secondary Endpoint measures and Follow-up Phase safety calls.

Medications and other non-medication interventions that are potential or available treatments for PTSD are also prohibited (e.g. stellate ganglion block, ketamine, neuromodulation, etc.) between Baseline and Primary Endpoint (Section 6.8 Concomitant Psychotherapy and Other Interventions).

Opioids other than hydrocodone, morphine, and codeine should be prohibited through Primary Endpoint due to the fact that such opioids may increase cardiovascular risk (e.g. QT interval prolongation).

6.7.5 Washout Parameters and Tapering Medications

All prohibited medications must be tapered and discontinued prior to the first Dosing Session. The required washout period following the last dose of a held/discontinued medication is determined by the medication's elimination half-life and its potential to cause psychiatric destabilization upon withdrawal.

A study clinician will check in with participants once weekly during their medication tapering period via phone to administer the C-SSRS, check for AEs, and concomitant meds. Preparation sessions can count as one of those check-ins.

Three categories of washout parameters apply:

Category 1 – Medications with Anticipated Psychiatric Concerns upon Withdrawal

Medications that may produce psychiatric symptoms or other concerns (e.g., rebound anxiety, mood instability, psychosis, seizure risk, or discontinuation syndrome) when withdrawn require a washout period of **5 elimination half-lives plus a minimum of 1 week (7 days) for clinical stabilization** after the last dose and prior to each Dosing Session. This extended washout ensures that both pharmacokinetic clearance and any emergent withdrawal-related psychiatric effects have adequately resolved before administration of the MDMA.

Clinical stability following completion of the washout period will be verified at the Medication Taper Phone Call (MT) prior to scheduling the Baseline CAPS-5-R and subsequent study procedures.

Medication classes in this category include, but are not limited to:

- Antidepressants (e.g., SSRIs, SNRIs, TCAs, MAOIs, atypical antidepressants)
- Antipsychotics (typical and atypical)
- Mood stabilizers (e.g., lithium, valproate, lamotrigine, carbamazepine)
- Benzodiazepines (e.g., alprazolam, clonazepam, diazepam, lorazepam)
- Barbiturates
- Other medications with known psychiatric discontinuation syndromes, as determined by the study medical provider

Category 2 – Medications without Anticipated Psychiatric Concerns upon Withdrawal

Medications that are not anticipated to produce clinically significant psychiatric symptoms or concerns upon discontinuation require a washout period of **5 elimination half-lives** after the last dose and prior to each Dosing Session. Because these agents do not carry a meaningful risk of psychiatric destabilization upon withdrawal, the additional stabilization period is not required; however, pharmacokinetic clearance must still be confirmed.

Medication classes in this category include, but are not limited to:

- Stimulants (e.g., amphetamine, methylphenidate, lisdexamfetamine)
- Non-benzodiazepine sleep aids without psychiatric withdrawal profiles (e.g., zolpidem, zaleplon), unless otherwise determined by the study medical provider
- Other prohibited medications without known psychiatric discontinuation syndromes, as determined by the study medical provider

Category 3 – Herbal Supplements

Participants should refrain from taking any herbal supplement (except with prior approval of the study team) for at least **1 week (7 days)** preceding each Dosing Session.

Clinical Considerations

The study medical provider will determine the appropriate washout category for each medication based on its pharmacological profile and the participant's clinical history. In cases where the categorization of a medication is ambiguous, the more conservative washout period (Category 1: 5 half-lives plus 7 days stabilization) should be applied.

Tapering schedules will be individualized in collaboration with the participant's prescribing provider and will follow a time course appropriate for the medication's pharmacokinetic and pharmacodynamic properties.

6.8 Concomitant Psychotherapy and Other Interventions

Participants are permitted to continue psychotherapeutic, psychiatric, and medical interventions that were established prior to study enrollment unless stated otherwise in this protocol. The restrictions described below are intended to minimize potential confounds to interpretation of the study data and to reduce safety risks associated with concurrent interventions during the active study period.

Permitted Interventions

If a participant is currently engaged with a psychotherapist or counselor outside of the study at the time of enrollment, the participant is permitted to continue regular outpatient psychotherapy sessions (e.g., individual therapy, couples therapy, or group therapy) in which they were already participating. Routine medical care not otherwise restricted by this protocol may also continue.

Prohibited Interventions

From Baseline through Primary Endpoint, participants should not initiate any new psychotherapeutic, psychiatric, or neuromodulatory intervention that they were not already engaged in at the time of enrollment. This restriction applies to both medication-based and non-medication-based treatments for PTSD or other psychiatric conditions, as these may confound interpretation of study outcomes or pose safety risks in combination with the study intervention. Prohibited interventions include, but are not limited to:

- New psychotherapeutic modalities or protocols (e.g., Cognitive Processing Therapy [CPT], Prolonged Exposure [PE], Eye Movement Desensitization and Reprocessing [EMDR], or other structured trauma-focused interventions not already underway at enrollment)
- Intensive outpatient programs (IOPs), partial hospitalization programs (PHPs), or residential treatment programs for psychiatric or substance use conditions
- Ketamine or esketamine (including ketamine-assisted psychotherapy)
- Stellate ganglion block

- Neuromodulation therapies (e.g., transcranial magnetic stimulation [TMS], electroconvulsive therapy [ECT], vagus nerve stimulation [VNS], transcranial direct current stimulation [tDCS])
- Psychedelic-assisted therapies or other investigational psychiatric interventions
- Hyperbaric oxygen therapy

This list is not exhaustive. Participants should consult the study team before initiating any new treatment during the study period. Prohibited medications are addressed separately in Section 6.7.4 Prohibited Medications.

Guidance for Outside Providers

If a participant's outside psychotherapist is providing ongoing supportive or maintenance-oriented psychotherapy, this may continue. However, the outside therapist should be discouraged from initiating a new psychotherapeutic modality, protocol, or evidence-based intervention (e.g., beginning a course of CPT or PE) that the participant was not already engaged in at the time of enrollment. The study team will communicate this guidance to outside providers, with the participant's consent, and will document any relevant communications.

Monitoring and Documentation

The study team will inquire about any changes in psychotherapeutic or other non-medication interventions at each study contact (see Table 3 and Table 4). All new or changed interventions will be documented on the appropriate case report form. Initiation of a prohibited intervention between Baseline and Primary Endpoint will be reviewed by the PI and Independent Safety Monitor to determine the appropriate course of action, which may include continuation in the study with documentation, delay of the next Dosing Session, or withdrawal from the study depending on the nature of the intervention and the clinical judgment of the PI.

After Primary Endpoint

Following the Primary Endpoint, participants will be permitted to resume or initiate psychotherapeutic, psychiatric, and medical interventions as clinically indicated in collaboration with their non-study outpatient providers.

7 Screen Failure, Discontinuation, Withdrawal, Termination, Dropout, Delay, and Halt

7.1 Screen Failures

Individuals who are screened for enrollment but do not meet inclusion or meet exclusion criteria are classified as screen failures. Individuals will be notified of their ineligibility, thanked for their willingness to participate, and will be encouraged to continue treatment with their primary mental health team. If the study team member doing the screening has any questions regarding applicability of inclusion and exclusion criteria, the case will be reviewed by the PI and/or designated study clinician as well as the Independent Safety Monitor. The PI will make the final determination regarding study eligibility. If requested by the screen failure non-participant, a

phone call with one of the study team members will be arranged for clarification. Any incidental findings discovered during screening will be referred to the appropriate service and level of care depending on the nature and acuity of the issue. If the participant is determined to be ineligible solely based on a criteria that is modifiable (e.g., uncontrolled hypertension), they will be informed of the reason why they are currently ineligible, and they will be invited back to restart the screening process once the modifiable criteria has been addressed. Otherwise, all other participants who are screen failures prior to enrollment during the Screening Phase will not be informed of why they were ineligible. Participants who are deemed ineligible after enrollment will be informed of why they were ineligible. All data gathered from a potential participant up until their screen failure will be kept, to include the reason for the screen failure.

7.2 Discontinuation of Study Intervention

If a participant must discontinue involvement in future Dosing Sessions for any reason (e.g., participant meets post-dosing cardiac or hepatic stopping criteria without meeting restart criteria), they will be permitted to complete the rest of the Integration Sessions in the current Intervention Cycle, complete all applicable safety labs, and will be asked to complete all assessments at Primary/Secondary Endpoints and Follow-up Phase safety calls on a schedule that is unchanged from if the participant did not have to discontinue the study intervention. The primary change to the schedule of activities in these cases is that subsequent Dosing Sessions will be replaced by a monthly safety call that follows the same procedures as the Follow-up Phase safety calls.

7.3 Participant Withdrawal from the Study

Withdrawal refers to a post-enrollment participant elects to no longer participate in the study. Any participant at any point during their enrollment may withdraw themselves for any reason (e.g. lack of desire to continue, change in military status, or permanent change of station, etc.) or may be withdrawn by PI and/or the appropriate health authority (i.e., DoD, FDA, or their representatives) for safety, behavioral, or administrative reasons. These reasons may include, but are not limited to: change in health status, inability to complete study procedures, unwillingness to maintain fidelity to procedures that ensure their safety, no longer meeting inclusion/exclusion criteria, etc.

Any participants who withdraw prior to the first dosing session will not be allowed to rejoin the study, will not be considered in the data analysis, and will not be counted in the enrollment goals, i.e. they can be replaced by a new participant. Any participant who withdraws at any point after the first dosing session will be considered a partial completer and included in the intent-to-treat analysis. In either case, an attempt will be made to contact the patient's primary mental health provider to inform them that the participant is no longer participating in the study and to provide a brief summary of their participation.

All participants who elect to withdraw from the study will be questioned about their reason for withdrawal. Participants are not obligated to provide a reason, and those who do not will be listed as “declined to answer” or “no reason given.” If a participant is withdrawn by the study team after enrollment, they will be offered an explanation as to why they can no longer participate and will be encouraged to return to routine standard of care treatment. All withdrawn

participants will be provided with a Study Exit Plan regardless of circumstances surrounding their withdrawal from the study (See Section 8.6.2 Study Exit Plan).

7.3.1 Pre-Randomization Early Termination

Pre-randomization Early Termination is when a participant is deemed eligible and enrolled in the study, but is later deemed ineligible prior to the first Dosing Session. These participants may fail to meet all inclusion criteria, may meet one or more exclusion criteria, or may withdraw consent prior to Enrollment Confirmation. The study team may also withdraw the participant for reasons described in Section 7.3 Participant Withdrawal From Study.

Participants who fail Enrollment Confirmation may not be re-enrolled into this study at a later date. All enrolled participants, even those failing Enrollment Confirmation, will be maintained in the database. Pre-randomization Early Terminations are not considered evaluable and are thus not included in the intent-to-treat analysis.

Pre-randomization Early Terminations may be identified through review of medical history, assessments, measures, laboratory results, or conversations with the participant. At any time during the Preparatory Period, if a potential participant is deemed to be ineligible in a non-modifiable manner, they are classified as a Pre-randomization Early Termination, notified they are not eligible for the study, and are not scheduled for additional assessments. These participants may be replaced per protocol.

7.3.2 Early Termination from the Study

Participants who are removed from the study after they are randomized and receive IP but do not complete the study may fall into one of these categories: *Post-randomization Early Termination* or *Dropout*. If the participant has received IP in at least one Dosing Session, they will be considered evaluable, included in the intent-to-treat analysis and all safety analyses, and will be invited to complete subsequent assessments. These participants will not be replaced.

If the study team makes the decision to terminate the participant from treatment or the study, they will explain the reason for withdrawal and document in the participant's source records and CRF. If a participant no longer meets all inclusion criteria or develops any exclusion criteria that, in the opinion of the Independent Safety Monitor or PI, affects the safety of the participant – including psychiatric diagnosis, medical diagnosis, pregnancy, or requiring use of prohibited medications – the participant will discontinue all subsequent Dosing Sessions and Intervention Cycles but remain in the study to complete Integration Sessions associated with their current Intervention Cycle.

Any time a participant terminates from the study early, the study team will attempt to obtain information about AE and concomitant medication outcomes if appropriate, as determined by the study physician and Independent Safety Monitor. The study team will provide the participant with a Study Exit Plan as described in Section 8.6.2.

7.3.2.1 Post-randomization Early Termination

Post-randomization Early Termination describes participants who discontinue study intervention but continue to participate in subsequent assessments at Primary and Secondary Endpoints. Data

collection will continue on the same schedule as planned through Study Completion visit procedures.

7.3.2.2 Dropout

If a participant decides to withdraw consent completely, they will be given the option to complete a final CAPS-5-R and study measures but may choose to terminate without further follow-up. These participants are defined as dropouts who withdraw consent due to any reason after receiving at least one dose of IP and no longer participate in the study (i.e., no further contact with investigators or study staff). Data collected on study participants up to the time of withdrawal of consent will remain in the trial database in order to maintain scientific validity.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to attend scheduled visits and are unable to be contacted by the site staff. If the participant has completed at least one Dosing Session, they will be included in the intent-to-treat analysis. All participants with at least one Dosing Session will be included in the safety analysis.

If a participant does not attend a scheduled visit, the study team will attempt to contact the participant to reschedule the visit as soon as possible and emphasize the importance of complying with the protocol specified visit schedule. The study team should determine if the participant is willing to comply with future visits.

If a participant does not respond to this initial contact, the study team will make multiple efforts to contact the participant and document each attempt in the source record. At least three attempts will be made via telephone over the course of approximately 7 days, with calls at different times of day. If telephone contact fails, an email should be sent if such contact information was provided. The emergency contact the participant provided should be contacted and asked to attempt contact with the participant. If the participant fails to respond to all of these contacts, they will be considered to have withdrawn from the study and are lost to follow-up.

7.5 Temporary Delays of Study Visits or Procedures

Each need to alter visit timing and or delay visits will be evaluated on a case-by-case basis with the primary determinants being to prioritize participant safety while maintaining fidelity to the study protocol to the extent feasible. In general, issues which can be resolved quickly such as minor illness, personal family issues, military occupational requirements, etc. will be allowed if they result in all requirements being achieved as close as feasible to the protocol-specified timeframe within +/- 1 week of the intended schedule. If delays are beyond the 1-week timeframe, the study team will respond on a case-by-case basis and inform the IRB if there is need for any modifications to the protocol.

Participants whose Dosing Sessions are delayed by unforeseen circumstances may restart any of their medications during the delay, as clinically indicated. When study visits resume, they will be given the option to resume Dosing Sessions after tapering off of these medications per Section 8.2.

7.6 Study Halt/Pause Criteria

Any of the following events will be cause for the study to be paused if they occur between the participant's first dose of MDMA and primary endpoint:

- Any Grade 5 events (death), for which relation to the study drug cannot be ruled out.
- The same IP-related Grade 4 (life-threatening) vitals (Appendix B), AEs (Appendix C), or lab values (Appendix D) (life-threatening) occurring in 3 participants or the similar Grade 4 event occurring in the same organ system in 3 participants that is possibly, probably, or definitely related to the IP (i.e., Grade 4 events that occur prior to IP administration would not be cause to pause the study unless determined otherwise by the Protocol Safety Review Team [PSRT], DSMB, IRB, Independent Safety Monitor [ISM], PI, or study sponsor).
- The same IP-related SAE (Section 9.13.4) occurring in 3 participants or similar SAEs occurring in the same organ system in 3 participants that is possibly, probably, or definitely related to the IP.

Any events that occur prior to IP administration would not be cause to pause the study unless determined otherwise by the PSRT, DSMB, IRB, ISM, PI, or study sponsor.

No new enrollment will occur during a study pause. Any currently enrolled participants will continue with their non-IP-related study activities as planned, unless the PSRT, DSMB, IRB, ISM, PI, or study sponsor otherwise determine that study activities may proceed. If a study pause criterion is met, a decision will be made based on the DSMB review as to whether enrollment in the study will be allowed to resume.

Study arm unblinding for an affected participant may be performed for above reviews if necessary.

7.7 Study Halt/Pause for Individual Participants

If any stopping criteria are met for an individual participant, the decision to restart or withdraw the participant will be made by the Principal Investigator in consultation with the Independent Safety Monitor and other medical experts as required. Any of the following events will trigger such a review if they occur between the participant's first dose of MDMA and primary endpoint:

- Any Grade 5 events (death), for which relation to the study drug cannot be ruled out.
- Any IP-related Grade 4 (life-threatening) vitals (Appendix B), AEs (Appendix C), or lab values (Appendix D.
- Any IP-related SAE (Section 9.13.4).

8 Study Phases and Procedures

Table 9. Screening Phase Study Visits

Screening Phase From Consent to Enrollment ~4 weeks (±2 weeks)		
Study Visit (Visit #/Visit Code)	**Visit Duration, Modality, & Timing**	**Brief Description of Events**
Screening (No visit numbers/ S_2, S_3, and S_4)	1-1.5 hour visits Mix of virtual, in-person, or asynchronous Multiple visits over 1 to 28 days	After initial prescreening questionnaire and phone call (S_1) which are not included in the 28-day screening phase, complete Informed Consent Form and HIPAA Authorization Form (S_2). S_3 will include two self report measures: SCID-5-SPQ and MPSQ. Clinician-administered screening will include SCID-5-PD (if indicated by SCID-5-SPQ screener), MINI, OSU-TBI, and C-SSRS (Lifetime and Last Month). Assess medical history and pre-study medications. Contact outside providers and order medical records, physical exam (PE), and conventional 12-lead EKG. Order screening labs via MHS Genesis to include urine drug and pregnancy screens, CMP, CBC, TSH, and T3/T4 (if abnormal TSH). Once all results and records are obtained, review along with notes from all screening visits and measures. Screening may take place over up to 28 days across multiple visits.
Enrollment (V1/EN)	0.5 hours Virtual or in-person 1-14 days after Clinician-Administered Screening (S_3) and Medical Screening (S_4) complete	Prior to enrolling: review screening measures, review medical history/records, discuss with outside providers, and conduct any clarification phone calls with the participant. Visit is 1.5 hours to review eligibility and medication tapering plan. If enrolled, begin medication tapering.

Abbreviations: AE, Adverse Event; CAPS-5-R, Clinician-Administered PTSD Scale for DSM-5 Revised; CBC, complete blood count; CMP, Complete Metabolic Panel; C-SSRS, Columbia-Suicide Severity Rating Scale; DUDIQ, Drug Use Desire and Intent Questionnaire; EKG, electrocardiogram; LEC-5, LEC-5, Life Events Checklist; MINI, Mini International Neuropsychiatric Interview; MPSQ, Medical Profile Status Questionnaire; OSU-TBI, Ohio State University Traumatic Brain Injury Identification Method; PCL-5, PTSD Checklist for DSM-5; SCID-5-SPQ, SCID-5 Self-report Personality Questionnaire; TSH, thyroid-stimulating hormone.

Table 10. Preparation Phase Study Visits

Preparation Phase with Enrollment Confirmation ~6 weeks (± 5 weeks)		
Study Visit (Visit #/Visit Code)	**Visit Duration, Modality, and Timing**	**Brief Description of Events**
Preparation Session 1 ($V2/P_1$)	2 hours (1.5 hours of therapy; 0.5 hour of measures) Virtual or in-person 0 to 12 days after Enrollment	90-minute Preparation Session with therapist. Target visit timing on tapering needs. If indicated, schedule calls between visits for tapering, safety, or further questions about medical history. Conduct medication reconciliation. Collect AEs, MPSQ, DUDIQ, PPS-Prospective, and C-SSRS (Last Month). A physical exam will be conducted by a qualified study clinician (if in-person). If Preparation Session 1 is not done in-person, the physical exam can be conducted at any in-person visit before the first Dosing Session.
Preparation Session 2 ($V3/P_2$)	2 hours (1.5 hours of therapy; 0.5 hour of measures) Virtual or in-person 2 to 21 days after Prep Session 1	90-minute Preparation Session with therapist. If tapering is complete or not needed, check eligibility and schedule upcoming visits. If tapering is ongoing, schedule a post taper call for ongoing assessment. Conduct medication reconciliation. Collect AEs, DUDIQ, PPS-Prospective, and C-SSRS (Since Last Visit). Conduct physical exam if in-person and not completed previously.
End of Medication Taper Phone Call (V4/MT)	1 hour Phone call 0 to 7 days after taper and stabilization end, or 0 to 7 days after P_2 if no medication taper required; up to 56 days after Enrollment; prior to Prep Session 3	If the participant was taking any psychiatric/psychoactive medications that were identified as needing to be tapered off, confirm medication taper and stabilization is complete. Medication taper for medications with drug-drug interactions **with** a psychiatric concern should occur at least 5 half-lives plus 1 week prior to Dosing Session 1. Medication taper for medications with drug-drug interactions **without** a psychiatric concern should occur at least 5 half-lives prior to Dosing Session 1. If participant *not* taking any medications that need to be tapered off, the study team may elect to not conduct this visit.

Preparation Phase with Enrollment Confirmation ~6 weeks (± 5 weeks)		
Study Visit (Visit #/Visit Code)	**Visit Duration, Modality, and Timing**	**Brief Description of Events**
		Assess AEs. Conduct C-SSRS (Since Last Visit). Conduct medication reconciliation. Begin process to schedule Baseline Independent Rater CAPS-5-R Session and Baseline Measures (B_1), Preparation Session 3 (P_3), and Dosing Session 1 (D_1). Study team conducts systematic eligibility check based on currently available data. If the participant meets criteria, schedule Baseline Independent Rater Session and Baseline Measures Visit (B_1), and Dosing Session 1 (D_1) via phone call if they have not already been scheduled. If the participant does not meet criteria, the study team will collaborate with the participant to address modifiable eligibility criteria. If eligibility criteria still cannot be achieved, the study team will initiate Pre-randomization Early Termination procedures.
Baseline Independent Rater Session and Baseline Measures Visit (V5/B_1)	1.5 hour for CAPS-5-R independent rater session, and 2-3 hours across 1-3 sessions within a 7-day period for all other baseline measures Virtual 0-14 days after MT	CAPS-5-R completed by an Independent Rater via telemedicine after taper is complete. CAPS-5-R scores shared with study team as soon as possible. Due to possibilities of negative side effects of withdrawal from psychiatric medications, the Baseline CAPS-5-R should be scheduled as close to the end of tapering as clinically appropriate so that participants who do not meet eligibility criteria can resume their previously prescribed medications as quickly as required for symptom management, and participants who do meet criteria can continue with the study intervention as soon as feasible. Study team conducts eligibility check based on CAPS-5 score and any new data since last eligibility check. If participant meets criteria, continue with study procedures. If the participant does not meet criteria, the study team will collaborate with the participant to address modifiable eligibility criteria. If eligibility criteria still cannot be achieved, the study team will initiate Pre-randomization Early Termination procedures. Complete self-reported measures to include: C-SSRS (Since Last Visit), MPSQ, BDI-II, PSQI, PEG, EASI (BAMHT Scale), BETS, HIT-6, NIH Toolbox, MIOS, MPFI-24, ACE, MSPSS, INQ-15, PIES, HPQSF, WHOQOL-BREF, WHODAS 2.0, SETS, AUDIT,

Preparation Phase with Enrollment Confirmation ~6 weeks (± 5 weeks)		
Study Visit (Visit #/Visit Code)	**Visit Duration, Modality, and Timing**	**Brief Description of Events**
		DUDIT, TLFB, STUQ, and DUQ (Baseline). Measures may be completed in 1-3 sessions within a 7-day period.
Preparation Session 3 (V6/P_3)	3 hours (1.5 hours therapy; 1.5 hours measures and lab collection) In-person 3 to 14 days after B_1 completed	Complete 90-minute Preparation Session with therapist. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), LEC-5, PCL-5, MPSQ, DUDIQ, PPS-Prospective, and WAI-SR. Collect baseline CMP, and Genomind pharmacogenetic cheek swab. Collect Neurable EEG data. If eligibility is not confirmed, do not randomize, and initiate Pre-randomization Early Termination.

Abbreviations: ACE, Adverse Childhood Experiences Questionnaire; AE, adverse event; AUDIT, Alcohol Use Disorders Identification Test; CAPS-5-R, Clinician-Administered PTSD Scale for DSM-5 Revised; CMP, complete metabolic panel; C-SSRS, Columbia-Suicide Severity Rating Scale; DUDIQ, Drug Use Desire and Intent Questionnaire; DUQ, Drug Use Questionnaire; EASI, Endorsed and Anticipated Stigma Inventory; EEG, electroencephalography; HIT-6, Headache Impact Test 6; HPQSF, HPQSF, Health and Work Performance Absenteeism and Presenteeism Short Form; INQ-15, Interpersonal Needs Questionnaire; LEC-5, Life Events Checklist; mDEQ-3, Modified Drug Effects Questionnaire; MIOS, Moral Injury Outcome Scale; MPFI-24, Multidimensional Psychological Flexibility Inventory-24; MPSQ, Medical Profile Status Questionnaire; MSPSS, Multidimensional Scale of Perceived Social Support; PCL-5, PTSD Checklist for DSM-5; PEG, Pain, Enjoyment of Life and General Activity Scale; PSQI, Pittsburgh Sleep Quality Index; STUQ, Smoking and Tobacco Use Questionnaire; TLFB, Timeline Follow-Back Calendar, Alcohol; WAI-SR, Working Alliance Inventory-Short Revised; WHOQOL-BREF, World Health Organization Quality of Life - BREF; WHODAS 2.0, World Health Organization Disability Assessment Schedule.

Table 11. Intervention Phase Study Visits

Intervention Phase From Randomization to Integration Session 3.3: 12 weeks (-3/+4 weeks)			
Intervention Cycle 1	**Study Visit**	**Visit Duration, Modality, and Timing**	**Brief Description of Events**
	Randomization (R)	0.5 hours Asynchronous Within 14 days of Baseline CAPS-5-R (B_1); After Preparation Session 3 (P_3); 12 to 48 hours before Dosing Session 1 (D_1)	Complete after Prep Session 3. Enter demographics into REDCap) for use in randomization. The participant does not need to be present for randomization procedures.
	Dosing Session 1 ($V7/D_1$)	6-8 hours In-person Within 15 days of Baseline CAPS-5-R (B_1)	8-hour Dosing Session with therapist with live audio-visual monitoring by supervising clinician. Administer 2 investigational capsules with 1 optional supplemental capsule 2 hours (±15 minutes) later unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications Prior to dosing: Conduct alcohol breathalyzer test and point-of-care urine drug and pregnancy screens. Collect baseline vital signs and Holter monitor EKG recording. Assess concomitant medications. Collect pre-dosing *and* at end of Dosing Session: C-SSRS (Since Last Visit) and CAM. Collect only at pre-dosing: EA-Pre Collect only at the end of Dosing Session: EA-Post and AEs. Collect blood pressure; heart rate; temperature; and Holter monitor EKG data at pre-dosing baseline, 2 hours (± 15 minutes) after initial

Intervention Phase From Randomization to Integration Session 3.3: 12 weeks (-3/+4 weeks)			
			dose but prior to supplemental dose, 4 hours (± 15 minutes) after initial dose, and at the end of the Dosing Session. Collect Neurable EEG data throughout Dosing Session.
	Integration Session 1.1 ($V8/I_{1.1}$)	2 hours (1.5 hours therapy; 0.5 hours measures and labs collection) In-person Morning after Dosing Session 1 (D_1)	90-minute Integration Session with therapist. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), DUDIQ, PPS-Retrospective, and mDEQ-3. Collect CMP. Conduct one 5-10 minute phone check-in between Integration Session 1.1 and 1.2 to assess for AEs and safety and address potential concerns. Collect Neurable EEG data.
	Integration Session 1.2 ($V9/I_{1.2}$)	2 hours (1.5 hours therapy; 0.5 hours measures collection) In-person or Virtual 3 to 14 days after Dosing Session 1 (D_1)	90-minute Integration Session with therapist. Review pre/post-dosing instructions for next Dosing Session. Schedule Dosing Session 2. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), DUDIQ, and PPS-Prospective. Conduct one 5-10 minute phone check-in between Integration Session 1.2 and 1.3 to assess AEs and safety and address potential concerns.

Intervention Phase From Randomization to Integration Session 3.3: 12 weeks (-3/+4 weeks)			
	Integration Session 1.3 ($V10/I_{1.3}$)	3 hours (1.5 hours therapy; 1.5 hours measures and lab collection) In-person 20 to 34 days after Dosing Session 1 (D_1); 1 to 7 days (ideally 1 day) before Dosing Session 2 (D_2)	90-minute Integration Session with therapist. Review pre/post-dosing instructions for next Dosing Session. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), and other measures: LEC-5, PCL-5, MPSQ, DUDIQ, PPS-Prospective, HIT-6, MIOS, MPFI, PEG, TLFB, STUQ, DUQ (Follow-Up), and WAI-SR. Collect CMP. Collect Neurable EEG data.
Intervention Cycle 2	Dosing Session 2 ($V11/D_2$)	6-8 hours In-person 21 to 35 days after Dosing Session 1 (D_1)	8-hour Dosing Session with therapist with live audio-visual monitoring by supervising clinician. Administer 2 investigational capsules with 1 optional supplemental capsule 2 hours (± 15 minutes) later unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications Prior to dosing: Conduct alcohol breathalyzer test and point-of-care urine drug and pregnancy screens. Collect baseline vital signs and Holter monitor EKG recording. Assess concomitant medications. Collect pre-dosing *and* at end of Dosing Session: C-SSRS (Since Last Visit) and CAM. Collect only at pre-dosing: EA-Pre Collect only at the end of Dosing Session: EA-Post and AEs. Collect blood pressure; heart rate; temperature; and Holter monitor EKG data at pre-dosing baseline, 2 hours (± 15 minutes) after initial dose but prior to supplemental dose, 4 hours (± 15 minutes) after initial dose, and at the end of the Dosing Session. Collect Neurable EEG data throughout Dosing Session.

Intervention Phase From Randomization to Integration Session 3.3: 12 weeks (-3/+4 weeks)			
	Integration Session 2.1 (V12/$I_{2.1}$)	2 hours (1.5 hours therapy; 0.5 hours measures and labs collection) In-person Morning after Dosing Session 2 (D_2)	90-minute Integration Session with therapist. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), DUDIQ, PPS-Retrospective, and mDEQ-3. Collect CMP. Conduct one 5-10 minute phone check-in between Integration Session 2.1 and 2.2 to assess for AEs and safety and address potential concerns. Collect Neurable EEG data.
	Integration Session 2.2 (V13/$I_{2.2}$)	2 hours (1.5 hours therapy; 0.5 hours measures collection) In-person or Virtual 3 to 14 days after Dosing Session 2 (D_2)	90-minute Integration Session with therapist. Review pre/post-dosing instructions for next Dosing Session. Schedule Dosing Session 3. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), DUDIQ, and PPS-Prospective. Conduct one 5-10 minute phone check-in between Integration Session 2.2 and 2.3 to assess AEs and safety and address potential concerns.
	Integration Session 2.3 (V14/$I_{2.3}$)	3 hours (1.5 hours therapy; 1.5 hours measures and lab collection) In-person 20 to 34 days after Dosing Session 1 (D_2); 1 to 7 days (ideally 1 day) before Dosing Session 3 (D_3)	90-minute Integration Session with therapist. Review pre/post-dosing instructions for next Dosing Session. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), and other measures: LEC-5, PCL-5, MPSQ, DUDIQ, PPS-Prospective, HIT-6, MIOS, MPFI, PEG, TLFB, STUQ, DUQ (Follow-Up), and WAI-SR. Collect CMP. Collect Neurable EEG data.
Intervention Cycle 3	Dosing Session 3 (V15/D_3)	6-8 hours In-person	8-hour Dosing Session with therapist with live audio-visual monitoring by supervising clinician. Administer 2 investigational

Intervention Phase From Randomization to Integration Session 3.3: 12 weeks (-3/+4 weeks)			
		21 to 35 days after Dosing Session 2 (D_2)	capsules with 1 optional supplemental capsule 2 hours (± 15 minutes) later unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications Prior to dosing: Conduct alcohol breathalyzer test and point-of-care urine drug and pregnancy screens. Collect baseline vital signs and Holter monitor EKG recording. Assess concomitant medications. Collect pre-dosing *and* at end of Dosing Session: C-SSRS (Since Last Visit) and CAM. Collect only at pre-dosing: EA-Pre Collect only at the end of Dosing Session: EA-Post and AEs. Collect blood pressure; heart rate; temperature; and Holter monitor EKG data at pre-dosing baseline, 2 hours (± 15 minutes) after initial dose but prior to supplemental dose, 4 hours (± 15 minutes) post initial dose, and at the end of the Dosing Session. Collect Neurable EEG data throughout Dosing Session.
	Integration Session 3.1 ($V16/I_{3.1}$)	2 hours (1.5 hours therapy; 0.5 hours measures and labs collection) In-person Morning after Dosing Session 3 (D_3)	90-minute Integration Session with therapist. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), DUDIQ, PPS-Retrospective, and mDEQ-3. Collect CMP. Conduct one 5-10 minute phone check-in between Integration Session 3.1 and 3.2 to assess for AEs and safety and address potential concerns. Collect Neurable EEG data.

Intervention Phase From Randomization to Integration Session 3.3: 12 weeks (-3/+4 weeks)			
	Integration Session 3.2 (V17/$I_{3.2}$)	2 hours (1.5 hours therapy; 0.5 hours measures collection) In-person or Virtual 3 to 14 days after Dosing Session 2 (D_2)	90-minute Integration Session with therapist. Conduct medication reconciliation. Collect AEs, C-SSRS (Since Last Visit), DUDIQ, and PPS-Prospective. Conduct one 5-10 minute phone check-in between Integration Session 3.2 and 3.3 to assess AEs and safety and address potential concerns.
	Integration Session 3.3 (V18/$I_{3.3}$)	2 hours (1.5 hours therapy; 0.5 hours measures collection) In-person or Virtual 20 to 35 days after Dosing Session 3 (D_3)	90-minute Integration Session with therapist. Discuss safety plan to include the participant reengaging care with their mental health provider(s) after secondary endpoint – to include potentially reengaging in therapy and psychiatric medication management. Conduct medication reconciliation and mental health treatment reconciliation. Collect AEs, C-SSRS (Since Last Visit), MPSQ, DUDIQ, and WAI-SR.

Abbreviations: AE, Adverse Event; CAPS-5-R, Clinician-Administered PTSD Scale for DSM-5 Revised; C-SSRS, Columbia-Suicide Severity Rating Scale; DUDIQ, Drug Use Desire and Intent Questionnaire; DUQ, Drug Use Questionnaire; EEG, electroencephalography; HIT-6, Headache Impact Test 6; LEC-5, Life Events Checklist; mDEQ-3, Modified Drug Effects Questionnaire; MIOS, Moral Injury Outcome Scale; MPFI-24, Multidimensional Psychological Flexibility Inventory-24; MSPSS, Multidimensional Scale of Perceived Social Support; PCL-5, PTSD Checklist for DSM-5; PEG, Pain, Enjoyment of Life and General Activity Scale; PSQI, Pittsburgh Sleep Quality Index; STUQ, Smoking and Tobacco Use Questionnaire; TLFB, Timeline Follow-Back Calendar, Alcohol; WAI-SR, Working Alliance Inventory-Short Revised; WHOQOL-BREF, World Health Organization Quality of Life - BREF; WHODAS 2.0, World Health Organization Disability Assessment Schedule.

Table 12. Follow-Up Phase Study Visits

Follow-up Period and Study Completion From Integration Session 3.3 until Study Completion: 6 months (± 2 weeks) after Dosing Session 3		
Study Visit (Visit #/Visit Code)	**Visit Duration/ Visit Timing**	**Brief Description of Events**
Primary Endpoint (V19/1°)	1.5 hour (CAPS-5-R IR assessment) and 3.5-4.5 hours (other primary endpoint measures) across 1-3 sessions within a 7-day period Virtual or in-person IR CAPS-5-R assessments and all other endpoint measures conducted 1-9 days after Integration Session 3.3 ($I_{3.3}$)	Occurs 77 to 119 days (14±3 weeks) post Baseline CAPS-5-R (B_1). Collect AEs, concomitant medications, and mental health treatment reconciliation. CAPS-5-R completed by independent rater. Measures include: TFA; LEC-5; PCL-5; C-SSRS (Since Last Visit); MPSQ, DUDIQ; BDI-II; PSQI; PEG; EASI (BAMHT Scale); HIT-6; NIH Toolbox; MIOS; MPFI-24; MSPSS; INQ-15; PIES; HPQSF; WHOQOL-BREF; WHODAS 2.0; TLFB (Alcohol); STUQ; DUQ (Baseline); DUQ (Follow-Up); Qualitative Interview. Measures may be completed across 1-3 sessions within a 7-day period.Review C-SSRS with participant and engage in safety planning as necessary.
Follow-up Safety Phone Calls ($V20/F_1$)	5-15 minutes Phone Phone call 3-5 weeks after Primary Endpoint (1°)	Follow-up safety phone call lasting 5-15 minutes 3-5 weeks after Primary Endpoint. Conduct medication reconciliation and mental health treatment reconciliation. Collect AEs, MPSQ, DUDIQ, and C-SSRS (Since Last Visit). Review C-SSRS with participant and engage in safety planning as necessary.

Follow-up Period and Study Completion From Integration Session 3.3 until Study Completion: 6 months (± 2 weeks) after Dosing Session 3		
Study Visit (Visit #/Visit Code)	**Visit Duration/ Visit Timing**	**Brief Description of Events**
Secondary Endpoint and Study Completion (V21/2°)	1.5 hour (CAPS-5-R IR assessment) and 2.5-3.5 hours (other endpoint measures) across 1-3 sessions within a 7-day period Virtual or in-person IR CAPS-5-R assessments and all other endpoint measures will be done 3 months (±2 weeks) after Dosing Session 3 (D_3)	Occurs 77 to 105 days (13 ± 2 weeks) after Dosing Session 3 (D_3). Conduct medication reconciliation and mental health treatment reconciliation. Collect AEs. CAPS-5-R completed by independent rater. Measures include: LEC-5; PCL-5; C-SSRS (Since Last Visit); MPSQ; DUDIQ; BDI-II; PSQI; PEG; EASI (BAMHT Scale); HIT-6; NIH Toolbox; MIOS; MPFI-24; MSPSS; INQ-15; PIES; HPQSF; WHOQOL-BREF; WHODAS 2.0; TLFB (Alcohol); STUQ; DUQ (Long Term Follow-Up). Measures may be completed across 1-3 sessions within a 7-day period. Complete blinding survey. Inform participants of unblinding procedures. Provide Study Exit Plan. Review C-SSRS with participant and engage in safety planning as necessary.

Abbreviations: AE, Adverse Event; BDI-II, Beck Depression Inventory-II; CAPS-5-R, Clinician-Administered PTSD Scale for DSM-5 Revised; C-SSRS, Columbia-Suicide Severity Rating Scale; DUDIQ, Drug Use Desire and Intent Questionnaire; DUQ, Drug Use Questionnaire; EASI (BAMHT Scale), Endorsed and Anticipated Stigma Inventory; HIT-6, Headache Impact Test 6; HPQSF, Health and Work Performance Absenteeism and Presenteeism Short Form; INQ-15, Interpersonal Needs Questionnaire; LEC-5, Life Events Checklist; mDEQ-3, Modified Drug Effects Questionnaire; MIOS, Moral Injury Outcome Scale; MPFI-24, Multidimensional Psychological Flexibility Inventory-24; MSPSS, Multidimensional Scale of Perceived Social Support; NIH, National Institutes of Health; OSU-TBI, Ohio State University Traumatic Brain Injury Identification Method; PCL-5, PTSD Checklist for DSM-5; PEG, Pain, Enjoyment of Life and General Activity Scale; PIES, Perceived Invalidation of Emotion Scale; PSQI, Pittsburgh Sleep Quality Index; SETS, Stanford Expectations of Treatment Scale; SCS-SF, Self-Compassion Scale Short Form; STUQ, Smoking and Tobacco Use Questionnaire; TFA, Theoretical Framework of Acceptability; TLFB, Timeline Follow-Back Calendar, Alcohol; WAI-SR, Working Alliance Inventory-Short Revised; WHOQOL-BREF, World Health Organization Quality of Life - BREF; WHODAS 2.0, World Health Organization Disability Assessment Schedule.

8.1 Screening Phase

Initial eligibility evaluation will consist of self-reported pre-screening (S_1), informed consent (S_2), clinician--administered screening measures (S_3), and medical screening (S_4) prior to enrollment (EN).

Screening will take place over multiple visits and will be completed in-person, via telemedicine, and/or over the telephone, within a maximum 28-day period which does not include pre-screening. All procedures must be completed but there can be some flexibility in timing and order of individual assessments. The following is the order of assessments:

- Initial eligibility, including self-report measures, discussions with participants and/or participant's providers, and review of medical records
- Clinician-administered screening assessments
- Medical assessments, including labs, EKG, and physical exam (any medical assessment results that are potentially exclusionary should be repeated within the 28-day Screening Phase to ensure reproducibility of the result prior to exclusion)

8.1.1 Pre-Screening (S_1)

Prospective participants will complete a prescreening questionnaire on their own on REDCap. The prescreening questionnaire will include demographics, LEC-5, PCL-5, and other self-report questions relevant to determining eligibility. If the prospective participant passes the initial eligibility check based on the prescreening questionnaire, they will be provided with the Informed Consent Form (ICF), HIPAA Authorization Form, and Pre/Post-Dosing Instructions, and Command Approval Form; and a prescreening phone call will be scheduled.

The prescreening phone call will involve an IRB-approved script to determine if the prospective participant meets basic eligibility criteria, will also involve a discussion about each of the documents that were previously sent, and will provide an opportunity for the participant to ask any initial questions about study enrollment. If the prospective participant meets initial prescreening eligibility criteria, they will be scheduled for the Informed Consent Visit (S_2). The prospective participant will be asked to complete the following on their own prior to the Informed Consent Visit (S_2): review each of the four documents, annotate questions for further discussion, and determine if there are any requirements of the study that they will be unable to agree to.

All individuals who are pre-screened should be assigned a Screening Number and recorded on the Pre-Screening Log. Data from potential participants who do not pass telephone screening will not be entered in the eCRF but basic demographics and reason of ineligibility will be documented on the Pre-screening Log. At any time during pre-screening, if a potential participant is deemed ineligible, they will be classified as a Pre-Screen Failure, notified that they are not eligible for the study, and not be scheduled for any additional Screening assessments.

8.1.2 Informed Consent (S_2)

If deemed potentially eligible after pre-screening, the prospective participant will meet with a trained and qualified study team member via telehealth or in-person visit to thoroughly explain, review, and discuss the ICF and HIPAA Authorization Form. They will also verify if there are

any elements of the Pre/Post-Dosing Instructions and Command Approval Form that they will be unable to agree to. The study team member will obtain written (or electronic) informed consent. The signature may be obtained using an electronic 21 CFR Part 11 compliant system. Additional screening and evaluation will not take place until the ICF is signed and completed. Once the ICF and HIPAA Authorization Form are completed, the participant will be invited to proceed with initial eligibility assessment procedures which will include self-reported screening measures, clinician-administered screening measures, and medical screening (See Sections 8.1.4, 8.1.5, and 8.1.6). If a participant fails Screening and is rescreened at a later date, a new copy of the ICF should be signed.

8.1.3 Informed Consent Process

The study will incorporate a single ICF per participant. However, the ICF will vary slightly based on whether the open-label lead-in training cohort is open for enrollment. When the open -label lead-in cohort is open, the ICF will describe the open-label procedures as well as the randomized cohort procedures. It will also provide the participants the option to opt in to one or both cohorts. When the open-label cohort is closed, the ICF will describe procedures and expectations for only the randomized cohort

After the potential participant has been contacted by study staff and has expressed interest in participating in the study, study staff will consent the potential participant with the ICF. If in--person, the consent will occur in a private office at WRNMMC Directorate of Behavioral Health. We would clarify to the participant that the ICF process is separate from clinical care. If virtual, a HIPAA-compliant and DoD-approved video conferencing platform will be used by study staff to consent the potential participant. During virtual consent procedures, both the study staff and the potential participant will utilize a private room to engage via the telemedicine platform in accordance with all appropriate telehealth policies and regulations.

The potential participant will be given a copy of the IRB-approved HIPAA authorization form and ICF describing in detail the study procedures and risks to read and review. The study staff will provide a full verbal explanation in the terms suited to the participant's comprehension of the purpose and objectives of the clinical trial. The protocol plan, study related visits, and tests/procedures, risks/benefits associated with clinical trial participation, and potential adverse events associated with participating in this study will be discussed. The eligibility requirements, rights as a study participant, costs, compensation, confidentiality, command authorization, and IRB contact information will also be discussed. Sufficient time will be given to the potential participant to ask and answer any questions before deciding on participation and to understand the study purpose and the types of health information that will be accessed, collected, and used by the research team. Potential participants will be given the opportunity to discuss the study with their family or think about it before agreeing to participate. Copies of the ICF and HIPAA authorization form will be provided so potential participants may review them at home before they decide upon participation. The informed consent process may take place over several visits. Potential participants will be given multiple opportunities to ask questions and have the study explained to them (and their family members or support persons if the potential participant chooses to do so).

Neither the investigator nor study staff will unduly influence or coerce a participant to participate in the study. Every effort will be made to eliminate the perception of authority, which is an important consideration when recruiting study participants who are currently in the military. To prevent coercion or perception of coercion, study staff will be in scrubs or civilian clothing and

will introduce themselves using non-military titles (e.g., "Dr.," "Mr.," "Ms."). The study team will confirm each participant's understanding of the consent and ensure understanding of what health information will be accessed or received, the purpose for the health information, and the uses of the health information.

The ability of each participant to provide and maintain informed consent will be an ongoing process throughout the study by study clinicians. To evaluate potential participant's understanding of information in the consent or what health information will be accessed or received, the purpose for obtaining the health information, and the uses of the health information, they will be asked to restate key study procedures, the general purpose of the clinical trial, and what they should do if they no longer wish to participate in the study. The research team may also ask additional questions to assess the potential participant's comprehension of the study, what health information will be accessed or received, the purpose of obtaining the health information, and the uses of the health information. For any gaps in the participant's understanding, study staff will review that information again with the participant and recheck for understanding until the participant demonstrates full understanding or study staff have concerns regarding participant comprehension. Any potential participant for whom informed consent – and comprehension of informed consent – cannot be established will not be included in the study.

After all questions have been answered and alternatives discussed, the ICF and HIPAA authorization form will be signed and dated by the participant and individual obtaining consent before further proceeding with any additional procedures for screening and enrollment. The consent process will be documented in the research record. The original signed ICF and HIPAA authorization form, in its entirety, will be maintained by the research staff at WRNMMC, and a complete copy of the signed ICF and HIPAA authorization form will be provided to the participant. Throughout the participant's participation in this study, each encounter provides an opportunity to continue the informed consent process. Throughout the study, study team members will continue to explain procedures specific to the study visits and the context of the specific visit in the overall course of the study. Participants will be given ample opportunity to ask questions throughout the study. Legally Authorized Representatives (LARs) will not be utilized in this study as all participants will undergo ongoing assessment of their ability to provide informed consent.

Participants will be informed of any new information made available from the sponsor, which may have an impact on their willingness to continue study participation. New information learned about the study will be communicated both verbally and in writing to the participant, and the conversation will be documented. Additionally, the informed consent will be updated to include new information learned and participants will be re-consented. Participants may withdraw consent at any time throughout the study.

Relevant medical and psychiatric records are required for the study physician to obtain a well -characterized medical history and assess eligibility. The study physician may need to contact the prescribing physician to discuss the tapering of medications (see Section 6.7 Concomitant Medications).

8.1.4 Self-Report and Clinician-administered Screening Measures (S_3)

SCID-5-SPQ is the only self-report measure participants will be asked to complete during S_3. Clinician-administered screening measures (S_3) will be administered by a qualified study clinician via telehealth or in-person and will include the following:

- SCID-5-PD for any personality disorders that screened positive on the SCID-5-SPQ.
- MINI to determine diagnosis of PTSD and other psychiatric comorbidities.
- C-SSRS (Lifetime and Last Month) to assess history of suicidal ideation and behavior.
- OSU-TBI to assess history of traumatic brain injury.

The study team will review the results of the clinician-administered screening measures and will determine eligibility. If deemed eligible, the participant will continue with their medical screening procedures if they have not yet been completed already. Findings of the clinician--administered screening measures may be verified throughout the Preparatory Period by ongoing clinical observation, but the measures will not be repeated. If the participant is not deemed eligible, they will proceed with procedures detailed in Section 7.1 Screen Failures.

8.1.5 Medical Screening (S_4)

Medical screening will occur 1-28 days after the Informed Consent visit and before enrollment. The physical exam must be performed by a qualified medical provider and lab assessments must be completed at an MHS lab. Depending on the participant's location, some or all of these assessments may be at MHS sites outside of WRNMMC. Medical assessments will include:

- Urine pregnancy test for females of childbearing potential
- Urine drug screen
- Blood pressure, pulse, and body temperature measurement
- Height and weight, which will be used to calculate Body Mass Index (BMI)
- Examination of head, eyes, ears, nose, throat, skin, heart, lungs, abdomen, and extremities
- Brief neurological exam (cranial nerves 2 to 12, sensory, motor, reflexes, and cerebellar function)
- Conventional 12-lead EKG
- Clinical laboratory assessments, per Section 9.11
- If there is evidence of significant hepatic disease, the prospective participant will not be eligible for enrollment and will be advised to see their personal physician for further evaluation.
- If the prospective participant has a condition such as controlled hypertension or Diabetes Mellitus (Type 2) that warrants additional testing to ensure they do not have evidence of significant vascular or other cardiac disease, they have no other evidence of cardiovascular or cerebrovascular disease by history, physical exam or EKG, and if the investigator judges their overall health and other cardiovascular risk factors to be acceptable (family history, smoking, lipid levels, body weight, level of physical activity), they will be referred for nuclear exercise testing by a cardiologist and for carotid ultrasound. If these tests fail to reveal evidence of significant vascular disease or other cardiac disease, the person may be enrolled if there are no other contraindications. Participants taking one or more antihypertensives may be enrolled in the study as long as their hypertension is controlled. The study team will record and review medications used to control hypertension prior to enrollment. Per the Independent Safety Monitor and

study physician's instruction, other tests of cardiovascular health and function may be required during screening, such as an echocardiogram. These will only be completed on a case-by-case basis to confirm a participant's cardiovascular eligibility.

Additional visits (in person, by telephone, or via telemedicine) may be scheduled at the discretion of the study staff to collect more information for determining eligibility or to discuss study expectations with the participant.

Once all results are obtained, the study team will review all medical assessments, notes from interviews and discussions, medical records, and measures against eligibility criteria. If, upon examination, there are questions raised about possible medical problems, the study physician will request additional medical assessments as indicated. The study physician may also contact outside providers with participant permission as needed.

Any medical screening results that are potentially exclusionary should be repeated within the 28-day Screening Phase to ensure reproducibility of the result prior to exclusion.

8.1.6 Meeting with Study Physician

A study physician will meet with the participant over telemedicine, the phone, or in-person to perform the following assessments:

- In advance of meeting with the participant, review medical and psychiatric history via review of provided records. If no records were provided or those provided are not sufficient, request additional records. Collect data on previous hospitalizations and healthcare utilization.
- Review medical and psychiatric history with the participant via interview, confirming information collected in medical records.
- Review past and current medications and adherence to prescriptions.
- Assess ability to become pregnant and discuss requirement for commitment to adequate birth control until the Primary Endpoint.
- Discuss medication taper.

If the physician deems the participant initially eligible based on these discussions and review of medical records, the participant will continue with clinician-administered screening assessments and/or medical screening if not already completed or continue with additional medical assessments as clinically indicated.

8.1.7 Enrollment (EN)

Once the participant completes clinician-administered and medical screening, the study team will have up to 14 days to review all notes from Screening visits, medical assessments, notes, discussions, medical records, and measures to check them against eligibility criteria and to notify the participant whether they are formally enrolled in the study. If they are not eligible, the study team will follow procedures detailed in Section 7.1 Screen Failures.

If the participant is eligible, Preparation Sessions 1 and 2 will be scheduled; medication tapering and concomitant medications dose adjustments will also be discussed with the participant and initiated, if applicable. The study team will consult the prescribing physician to formulate and initiate medication tapering for participants. For more details on concomitant medications, tapering, and allowed/prohibited medications, refer to Section 6.7 Concomitant Medications.

8.2 Preparation Phase

The Preparation Phase will include three 90-minute Preparation Sessions (P_{1-3}), medication tapering and phone call (MT) if needed, and baseline measures (B_1) prior to the Intervention Phase which will begin with randomization and the first Dosing Session (D_1). The Preparation Phase will be initiated by the first Preparation Session within 12 days of Enrollment and may last 1 to 11 weeks (anticipate typically 2-4 weeks), primarily dependent on duration of medication tapering. There must be at least 2 days between Preparation Sessions.

During the Preparation Sessions, study therapists will follow adherence criteria per the Treatment Manual. During these visits, the therapist will work with the participant to prepare for the first Dosing Session, build a therapeutic alliance, and promote a safe mindset and setting for processing trauma-related memories, emotions, and thoughts.

At any time during the Preparation Phase, if a potential participant is deemed to be ineligible in a manner that is non-modifiable, the study team will classify the participant as a Pre-randomization Early Termination (see Section 7.3.1 Pre-randomization Early Termination), notify the potential participant that they are ineligible for the study, and not schedule additional assessments.

8.2.1 Preparation Sessions 1 and 2 (P_1 & P_2)

Purpose – Preparation Sessions between the therapist and participant will focus on developing the therapeutic alliance; obtaining the background for the trauma(s); promoting a safe mindset and setting for processing trauma-related memories, emotions, and thoughts; and preparing the participant for the first Dosing Session (D_1) while integrating principles of ACT per the Treatment Manual.

Timing –

- Preparation Session 1 (P_1) will occur 0 to 12 days after Enrollment. The visit timing should take into account appropriate times for monitoring medication tapering.
- Preparation Session 2 (P_2) will occur 2 to 21 days after Preparation Session 1 (P_1). The visit timing should take into account appropriate times for monitoring medication tapering.
- Both Preparations Session 1 and 2 may be conducted in-person or via secure telehealth.

Personnel – Preparation Sessions will be conducted by the therapist.

Procedures – At each 90-minute Preparation Session, the therapist will:

- Inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements. Record AEs as described in Section 9.13 Adverse Events, Serious Adverse Events, Adverse Events of Special Interest and Other Safety Reporting.
- Inquire about concomitant medication use and adherence.
- Confirm that medication tapering has completed, as appropriate.
- Review Pre/Post-Dosing Instructions with the participant.
- Discuss goals and expectations for Dosing Session 1 (D_1), following standard procedures and techniques described in the Treatment Manual.
- Confirm eligibility by reassessing specified eligibility criteria.
- Record the therapy session.

Other Procedures – Qualified study team members will:

- Collect measures per Table 6.
- Collect baseline CMP and pharmacogenetic cheek swab.
- Conduct physical exam if in-person and a qualified study medical provider has not done so already. The physical exam can be conducted at any in-person visit before the first Dosing Session.
- Call the patient between visits if indicated for tapering, safety, or any further questions about medical history.

Next Steps –

- If eligibility criteria have been met with available data thus far, participants who are still tapering off specified medications may continue with medication tapering, and study team will schedule Medication Tapering Phone Call (MT) within 7 days of completion of tapering and stabilization. If medication tapering and stabilization have already been completed, proceed with systematic eligibility check.
- If the participant does not meet criteria, the study team will collaborate with the participant to address modifiable eligibility criteria. If eligibility criteria still cannot be achieved, the study team will initiate Pre-randomization Early Termination procedures (see Section 7.3.1). All data collected to date will be retained for analysis unless otherwise restricted by the sponsor.

8.2.2 Medication Taper Phone Call (MT)

If participant is *not* taking any medications that need to be tapered off, the study team may elect to not conduct this visit.

Purpose – The MT is conducted to confirm that tapering of prohibited psychiatric or psychoactive medications has been completed in accordance with study protocol, and that participants are clinically stable and eligible to proceed with the Baseline CAPS-5-R assessment.

Timing – The call will occur 0 to 7 days following the end of the taper and stabilization period, and no later than 56 days after enrollment. If no medications need to be tapered, or if all medications have been successfully tapered off prior to P_2, the medication taper phone call will occur 0 to 7 days after P_2. It must be completed prior to Preparation Session 3 and the Baseline CAPS-5-R assessment.

Personnel – This phone call will be conducted by a qualified study medical provider.

Procedures –

- *Conduct Systematic Eligibility Check:* Ensure participant continues to meet eligibility criteria with currently available information.
- *Verify Medication Taper and Stabilization:* Confirm that the participant has completed tapering of prohibited medications and has remained off these medications for a sufficient period (typically ≥5 half-lives plus at least 7 days for stabilization for medications with a psychiatric concern). Medication taper for medications with drug-drug interactions without a psychiatric concern should occur at least 5 half-lives prior to Dosing Session 1.
- *Review of Concomitant Medications:* Conduct medication reconciliation to confirm that no prohibited substances or unapproved medications are being taken, including herbal supplements and non-prescription medications.

- *Assess for Adverse Events:* Evaluate and document any withdrawal symptoms or other adverse effects experienced during or following taper.
- *Assess for Suicidality:* Conduct C-SSRS (Since Last Visit).
- *Plan Next Steps:* See Next Steps below.

Next Steps –

- If participant meets eligibility criteria, is stable, and is ready to proceed, begin process to schedule the Baseline CAPS-5-R Independent Rater Session and Baseline Measures Visit (B_1), Preparation Session 3 (P_3), and Dosing Session 1 (D_1) any other pending assessments contingent on participant eligibility.
- If tapering is incomplete, or if the participant is experiencing unstable symptoms, the study team will delay further study activities until the participant is reassessed. An additional follow-up call may be scheduled within 7 days based on clinical judgment. Participants not meeting criteria may be withdrawn or classified as a Pre-randomization Early Termination (see Section 7.3.1) if tapering is unsuccessful within protocol timelines.

8.2.3 Baseline CAPS-5-R Primary Outcome Independent Rater Assessment (B_1)

Baseline CAPS-5-R Purpose – A blinded independent rater will conduct the CAPS-5-R to establish a baseline symptom severity score prior to randomization.

Timing – The Baseline CAPS-5-R independent rater assessment (B_1) must occur:

- After completion of Preparation Sessions 1 and 2.
- If applicable, after completion of medication tapering and stabilization period with associated Medication Taper Phone Call.
- Within 56 days of enrollment.
- Via secure telehealth.

Additional considerations for timing:

- Due to possibilities of negative side effects of withdrawal from psychiatric medications, the Baseline CAPS-5-R should be scheduled as close to the end of tapering as clinically appropriate so that participants who do not meet eligibility criteria can resume their previously prescribed medications as quickly as required for symptom management and participants who do meet criteria can be enrolled and treated as quickly as possible.
- The Baseline CAPS-5-R assessment should also be scheduled as close as feasible to the first Dosing Session which may be scheduled 15 days after.

Personnel – The CAPS-5-R must be administered by an independent, blinded clinician trained in the use of the CAPS-5-R and the study procedures. The assessor should have no involvement in therapy or medication management to preserve blinding.

Procedures –

- The blinded independent rater will conduct the CAPS-5-R with the participant.
- The assessment will be conducted via secure telehealth platform.
- This visit may be recorded to establish inter-rater reliability.
- The raters will enter the scores into the database and notify the core study staff whether the participant meets criteria for PTSD per CAPS-5-R and has a CAPS-5 total severity score (integrated within CAPS-5-R) of 26 or greater, indicating moderate PTSD.

- The core study team will conduct an eligibility check to verify participant still meets criteria for continued enrollment.

Next Steps –

- If the participant meets criteria, proceed with Preparation Session 3 (P_3) and Dosing Session 1 (D_1) which should already have been scheduled. If these sessions have not already been scheduled, schedule them via phone call or asynchronous communication.
- If the participant does not meet criteria, the study team will collaborate with the participant to address modifiable eligibility criteria. If eligibility criteria still cannot be achieved, the study team will initiate Pre-randomization Early Termination procedures. All data collected to date will be retained for analysis unless otherwise restricted by the sponsor.

8.2.4 Baseline Measures (B_1)

Purpose – For participant to complete self-report measures.

Timing – The Baseline Measures (B_1) must occur:

- After completion of Preparation Sessions 1 and 2.
- If applicable, after completion of medication tapering and stabilization period with associated Medication Taper Phone Call.
- Across 1-3 sessions within a 7-day period.
- In-person or via secure telehealth.

Personnel – A qualified study team member.

Procedures –

- Once appropriate conditions are met, a qualified study team member will provide the participant with access to the self-report measures for the participant to complete.

8.2.5 Preparation Session 3

Purpose – Preparation Sessions between the therapist and participant will focus on developing the therapeutic alliance; obtaining the background for the trauma(s); promoting a safe mindset and setting for processing trauma-related memories, emotions, and thoughts; and preparing the participant for the first Dosing Session (D_1) while integrating principles of ACT per the Treatment Manual.

Timing – Preparation Session 3 (P_3) will:

- Occur 3 to 14 days after Baseline CAPS-5-R Independent Rater Assessment (B_1) is completed.
- Be scheduled 1-4 days prior to Dosing Session 1 (D_1), ideally 1 day prior to D_1.
- Be conducted in-person.

Personnel – Preparation Sessions will be conducted by the therapist. Other study procedures will be conducted by qualified study team members.

Procedures – During the 90-minute Preparation Session, the therapist will:

- Inquire about any possible changes in health to ensure the participant continues to meet all eligibility requirements. Record AEs as described in Section 9.13 Adverse Events, Serious Adverse Events, Adverse Events of Special Interest and Other Safety Reporting.
- Inquire about concomitant medication use and adherence.
- Confirm that medication tapering has completed, as appropriate.
- Medication taper for medications with drug-drug interactions without a psychiatric concern may still be ongoing at Preparation Session 3 (P_3) because they should be tapered off at least 5 half-lives prior to Dosing Session 1 (D_1).
- Review Pre/Post-Dosing Instructions with the participant.
- Discuss goals and expectations for Dosing Session 1 (D_1), following standard procedures and techniques described in the Treatment Manual.
- Confirm eligibility by reassessing specified eligibility criteria.
- Record the therapy session.

Other Procedures – Qualified study team members will:

- Collect measures per Table 6.
- Collect baseline BMP, liver panel and Genomind pharmacogenetic cheek swab.
- Collect Neurable EEG data.
- Conduct physical exam if a qualified study medical provider has not done so already.
- Call the patient between visits if indicated for tapering, safety, or any further questions about medical history.
- If tapering is ongoing at Preparation Session 3 (P_3), the study team will schedule a telephone phone call after completion of tapering. If tapering is complete or not needed, the participant may proceed with Dosing Session 1 (D_1).

Next Steps –

- If all eligibility criteria have been met, and no preclusions to dosing have been identified, the participant may proceed with Dosing Session 1 (D_1).
- If the participant does not meet criteria, the study team will collaborate with the participant to address modifiable eligibility criteria. If eligibility criteria still cannot be achieved, the study team will initiate Pre-randomization Early Termination procedures (see Section 7.3.1). All data collected to date will be retained for analysis unless otherwise restricted by the sponsor.

8.3 Pre/Post-Dosing Instructions, Support Persons, and Overnight Stays

8.3.1 Pre-Dosing Instructions

As noted in Section 5.3 Lifestyle Modifications, the Pre/Post-Dosing Instructions will be provided to the participant upon completing the study informed consent. The Pre/Post-Dosing Instructions will then be reviewed with the participant at the following encounters: Preparation Sessions 1, 2, and 3; Integration Sessions 1.2, 1.3, 2.2, and 2.3.

Leading up to each Dosing Session, the participant must:

- Take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each Dosing Session.
- Not use nicotine (neither recreational nor medical) after 12:00 A.M. (midnight) the evening before each Dosing Session and not until the day after each Dosing Session.

- Not use caffeine or alcohol 24 hours before each Dosing Session and not until at least the day after each Dosing Session.
- Refrain from the use of any psychoactive medication or substance not approved by the research team from Baseline through final Dosing Session.
- Comply with medication requirements per protocol (refer to Section 6.7 Concomitant Medications). Medications will only be discontinued after enrollment per clinical judgment of the site physician in consultation with the prescribing physician.
- Decrease dose of allowable opiates (per Section 6.7 Concomitant Medications), if used for pain management, leading up to the Dosing Session in order to avoid taking the medication prior to each Dosing Session and 24 hours after. During this period, the participant will be allowed to take the medication if needed for intolerable pain flare-ups or to prevent withdrawal symptoms.
- Refrain from each of the following for at least 1 week before each Dosing Session:
    - Taking any supplement (except with prior approval of the research team).
    - Taking any nonprescription or over-the-counter medications (with the exception of non-steroidal anti-inflammatory medications or acetaminophen unless with prior approval of the research team).
    - Taking any prescription medications without approval from the study team (with the exception of birth control, thyroid hormones, or other medications approved by the study team).
- Refrain from the following foods or dietary practices for the duration of the study due to potential false positive urine drug screens or other issues that could lead to canceling a Dosing Session:
    - Poppy seeds
    - Hemp or CBD products
    - Tonic water
    - Kombucha or fermented beverages
    - Coca tea
    - Ketogenic diet
    - Very low carbohydrate diet
    - Fasting
    - Dehydration
- Proactively inform the study team if any of these requirements cannot be met.
- Receive approval from study physician regarding any exception to these requirements.

8.3.2 Post-Dosing Instructions

After each Dosing Session, the participant must:

- Not drive after each Dosing Session until after the Integration Session the next morning.
- Either:
    - Remain overnight at the study site after each Dosing Session until after the Integration Session the next morning.
        - Study staff will escort participants to their lodging if the participant chooses to stay on base.
    - Identify a Support Person willing to accompany them overnight at a safe lodging of their choice after each Dosing Session, and have the Support Person escort the participant to that safe lodging from the study site in the evening after the Dosing Session and to the study site the following morning for the Integration Session.

8.3.3 Support Person

Participants in this study may have a "Support Person" (i.e., a loved one, caregiver, friend, or non-medical attendant) assist them in the study. Although a Support Person's role is to further enhance safety and adherence to study protocols, having a Support Person is not a requirement for participation in the study.

During the Screening and Preparatory Phases, the participant will be encouraged to identify an appropriate Support Person to 1) escort the participant to and from Dosing Sessions and 2) stay with the participant overnight after Dosing Sessions. In advance of a Dosing Session, any Support Person spending the night with the participant will be provided with a handout of instructions to orient them to the role. The handout will include contact information of the study team and what to do in the case of an emergency. The participant will also provide the study team with the name and contact information for their Support Person(s) in advance of each Dosing Session.

If the participant is lodging on Naval Support Activity Bethesda (NSAB) in a study-designated accommodation for the night after a Dosing Session, a Support Person is not required but still encouraged to stay. When there is no Support Person to escort the participant to their study-designated NSAB lodging, a study team member will escort the participant to their lodging.

If the participant is lodging anywhere other than a study-designated accommodation on NSAB for the night after a Dosing Session, the participant must have a Support Person to 1) escort the participant to and from the Dosing Session, 2) stay with the participant overnight after the Dosing Session, and 3) drive the participant back in the next morning for the Integration Session.

If a participant would like a Support Person present for a brief portion of any Preparation, Dosing, or Integration Session, a meeting between the therapist and the Support Person will be scheduled prior to the Dosing Session. There must be mutual agreement between the participant, study therapist, and Support Person concerning the scope of the Support Person's involvement.

8.3.3.1 Orienting the Support Person

The participant's designated study therapist will conduct a documented Support Person Orientation. This touchpoint is intended to establish rapport, ensure the Support Person understands their role in the participant's safety plan, and confirm their availability for transportation and transition of care as needed.

The following items will be included in the instructions orienting the Support Person to their role. These items are recommendations for the Support Person to consider as appropriate for the evening of and morning after the participant's Dosing Session:

- Assist the participant in adhering to their Pre/Post-Dosing Instructions to the extent feasible.
- Avoid initiating potentially stressful conversations the evening after dosing.
- Be aware that the participant may not want to discuss their experience. If they do want to share their experience, provide nonjudgmental, empathetic support without interpreting their experience.
- Keep all participant information confidential.
- Ensure the participant has a comfortable place to sleep and discuss the plan for dinner, wakeup, breakfast, and travel time for the next day's therapy session.

- Ensure that the participant does not consume non-prescribed drugs or alcohol on the day prior to and the evening after the Dosing Session.
- Remain sober throughout the entire overnight stay.
- Ensure that phone/computer time is limited the evening before and after each Dosing Session to minimize impact on sleep.
- Ensure that the participant does not leave the overnight accommodation without accompaniment.
- Ensure that the participant is not left alone in their overnight accommodation without accompaniment. The participant may have privacy at the overnight accommodation.
- Remain available to support the participant's needs overnight.

The study therapist will document the date, duration, and key outcomes of this orientation within the Participant's Study Source Record. This documentation should indicate that the Support Person has been adequately briefed on the transition of care, safety requirements, general recommendations for ensuring the participant has a restful evening following their dosing session. The Source Record should document that the Support Person verbally acknowledges and understands the instructions outlined above.

8.3.4 Overnight Stays

The study will provide participants with the option to stay overnight on the study site in suite rooms reserved for the study in Tranquility Hall next to WRNMMC. The overnight stay at the study site is included in the study protocol primarily as an opportunity for rest in a relaxed environment away from the distractions of home and to mitigate logistical barriers to participate in the Integration Session at the study site the morning following each Dosing Session. The overnight stay is not required for medical reasons, but in case of emergencies, the study physician is on-call 24 hours per day.

If the participant is not lodging in a study-designated lodging on NSAB, participants must identify a Support Person to escort them to their lodging on the evening of the Dosing Session and to escort them to the Integration Session the morning after the Dosing Session. Participants and Support Persons must stay overnight in the same geographic region as the study site.

8.4 Intervention Phase

During the Intervention Phase, which occurs over a duration of approximately 9 to 15 weeks, participants will complete three Intervention Cycles. Each Intervention Cycle consists of a Dosing Session, followed the morning after by the first Integration Session ($I_{1.1}/I_{2.1}/I_{3.1}$), one phone follow-up between the first and second Integration Session, a second Integration Session ($I_{1.2}/I_{2.2}/I_{3.2}$) 3-14 days after the most recent Dosing Session, a second phone follow-up between the second and third Integration Session, and a third Integration Session ($I_{1.3}/I_{2.3}/I_{3.3}$) 20-34 days (20-35 days for $I_{3.3}$) after the most recent Dosing Session. The three Dosing Sessions will be scheduled three to five weeks apart. See Table 4 and Table 11 for more details.

8.4.1 Dosing Sessions

There will be three double-blinded Dosing Sessions. Procedures for the intervention will remain the same across all sessions and all procedures regardless of dose received. Dosing Sessions will be eight hours long, measured from 30 minutes prior to IP administration. The Dosing Sessions will consist of:

- **Dosing Session 1 (D_1)**: will occur within 15 days of the Independent Rater CAPS-5-R assessment (B_1) and 1 to 4 days after Preparatory Session 3 (P_3). The first Dosing Session will involve initial administration of 2 capsules (total of 80 mg MDMA or 40 mg MDMA). The initial dose will be followed by an optional supplemental dose of 1 capsule (40 mg MDMA or inactive placebo) 2 hours (±15 minutes) after the initial dose unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications
- **Dosing Session 2 (D_2)**: will occur 21 to 35 days after Dosing Session 1 (D_1) and 1-7 days (ideally 1 day) after Integration Session 1.3 ($I_{1.3}$). The second Dosing Session will also involve initial administration of 2 capsules (120 mg MDMA or 40 mg MDMA). An optional supplemental dose of 1 capsule (60 mg MDMA or inactive placebo) will be administered 2 hours (±15 minutes) after the initial dose unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications
- **Dosing Session 3 (D_3)**: will occur 21 to 35 days after Dosing Session 2 (D_2) and 1-7 days (ideally 1 day) after Integration Session 2.3 ($I_{2.3}$). The third Dosing Session will involve variable dosing in that the dose of study drug will be decided in collaborative shared decision-making between the participant, therapist, and study medical provider; this decision will consider factors such as tolerability, AEs, risks, and benefits based on the previous two dosing sessions. The participant will initially be administered 2 capsules (80 or 120 mg MDMA or 40 mg MDMA, based on the aforementioned shared decision-making). A supplemental dose of 1 capsule (40 or 60 mg MDMA or inactive placebo) will be administered 2 hours (±15 minutes) after the initial dose unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications

Table 13. Schedule of Procedures for Dosing Sessions

Approximate Time	Procedures
0800	● Participant arrives
0800-0900	● Collect POC urine drug screen (and pregnancy test if applicable), alcohol breathalyzer. ● Check last use of nicotine, alcohol, and caffeine. ● Collect concomitant medications information, AEs, EA-Pre, C-SSRS (since last visit), and baseline CAM. ● Collect baseline vitals (blood pressure, pulse, and body temperature) and Holter monitor EKG recording. ● Begin EEG recording.
0900	● Begin audio/video recording. ● **Offer initial dose of 2 capsules** for participant to self-administer.
1100	● Collect vitals (blood pressure, pulse, and body temperature) and Holter monitor EKG recording, both prior to supplemental dose being offered.

	• **Offer supplemental dose of 1 capsule** to be self-administered, unless tolerability issues emerge with the first dose or if it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications
1300	• Collect vitals (blood pressure, pulse, and body temperature) and Holter monitor EKG recording
1600-1630	• Collect vitals (blood pressure, pulse, and body temperature) and Holter monitor EKG recording. • Collect AEs, EA-Post, C-SSRS (since last visit), and CAM. • If CAM not returned to baseline, readminister CAM every 10 minutes. If CAM returned to baseline, discharge patient to escort.

Abbreviations: AE, adverse event; CAM, Confusion Assessment Method; C-SSRS, Columbia-Suicide Severity Rating Scale; EA-Post, Euphoria Assessment Post-Dosing; EEG, electroencephalography; EKG, electrocardiogram; POC, point-of-care.

Note: All times have a window of ±15 minutes unless stated otherwise.

8.4.1.1 Pre-IP Administration Procedures

- 12 to 48 hours prior to the first Dosing Session, the participant will be randomized using REDCap (see Section 6.4.1).
- 12 to 48 hours prior to each Dosing Session, the study team will obtain the container assignment from the investigational pharmacy.
- On the day of the Dosing Session, the participant will arrive approximately 60 minutes prior to IP administration.
- The study team will ensure the participant has not used nicotine or ingested anything except alcohol-free liquids since midnight, has not used alcohol or caffeine 24 hours before the Dosing Session, and has complied with all other Pre-Dosing Instructions (see Section 8.3.1).
- The study team will remind the participant that they are not permitted to use nicotine, alcohol, or caffeine at least until the day after each Dosing Session.
- The study team will complete urine drug screen, pregnancy test, alcohol breathalyzer test, and concomitant medication review.
    - A positive drug screen or a positive breathalyzer will be reviewed by the study physician and may be cause for delaying IP administration to a later time, rescheduling the session to a later date, or withdrawing the participant from the study, based on Independent Safety Monitor review.
    - A positive pregnancy screen is cause for withdrawal from the protocol.
- A qualified study team member will collect baseline vital signs (blood pressure, pulse, and body temperature) and Holter monitor EKG recording.
- The therapist will collect EA-Pre, Since Last Visit C-SSRS, and baseline Confusion Assessment Method (CAM).
- The therapist will review procedures for the Dosing Session with the participant, discuss the participant's intentions and concerns, and review strategies to navigate some of the commonly experienced effects of MDMA.
- If the participant continues to be eligible, the session will proceed.

8.4.1.2 During the Dosing Session

- After video recording has begun, a qualified staff member will provide the participant with the initial dose of IP to self-administer with an electrolyte-containing fluid.
- A supervising clinician will be monitoring a live video feed of the room throughout the session and will be in a separate private monitoring room within 30 seconds walking distance from the dosing room (the monitoring room will be 1-5 doors down in the same hallway as the 5 dosing rooms).
- The participant will be in a private clinical room with their study therapist and will sit or recline on comfortable furnishings. Eyeshades and a program of music will be provided for the participant if they wish to use them. Whenever they wish, participants may speak to the therapist, who will provide guidance and support, as needed.
- After the first hour, if the participant has not spoken spontaneously, the therapist will check in with them about the nature of the experience. For the rest of the experience, as appropriate, the therapist will support and encourage the participant in emotional processing and resolution of whatever psychological material is emerging, as described in the Treatment Manual.
- Electrolyte-containing fluids will be provided throughout the session but not to exceed three liters overall.
- Vital signs and 6-lead Holter monitor EKG recording will be collected multiple times throughout the session: at pre-dosing, at 2 hours (± 15 minutes) after the initial dose before the supplemental dose is administered, at approximately 4 hours (± 15 minutes) after the initial dose, and the last measurement at the end of the session.
- If the participant is not administered the supplemental dose, the study team will document the reason.
- The study physician will be contacted with a brief description of how the session is progressing and the recent vital signs. The study physician will approve or deny the administration of the supplemental dose. If an AE requiring medical attention has occurred between the initial and supplemental dose, the study physician will determine whether the supplemental dose is recommended or not. If medical attention is needed, the study physician will provide further instruction or consult the Independent Safety Monitor.
- A supplemental dose will be administered with a glass of electrolyte-containing fluid 2 hours (± 15 minutes) after the initial dose, unless tolerability issues emerge with the first dose or it is declined by the participant. Decision-making regarding dosing will be performed by a licensed professional who is credentialed to prescribe mental health medications
- Food may be provided during the latter part of the session.
- If there is an approved Support Person, that person may arrive as agreed upon but will wait in the waiting room until the therapist brings them into the session room. Alternatively, they may arrive after the session has ended.

8.4.1.3 End of Dosing Session

- The therapist will administer EA-Post and Since Last Visit C-SSRS.
- The therapist will record AEs and concomitant medications.

- The participants should be considered recovered and ready for discharge when all medical and psychiatric parameters are acceptable, elevations in vital signs have resolved to pre-IP levels, the participant is alert, ambulatory, and emotionally stable.
    - Vital signs have returned to pre-dosing baseline (or within 20% over baseline if provider approves).
    - Modified CAM has returned to pre-dosing baseline.
    - The participant is able to stand upright and ambulate as appropriate for age and condition.
- The therapist will provide and review the Post-dosing Instructions with the participant.
- The study team will verify that the participant will have a mode of transportation home that does not require that they drive. Transportation services such as Uber, Lyft, taxi, or similar ridesharing are not acceptable unless the participant has an individual who will escort them to their place of stay.
- A member of the study team shall remain available to participants via 24-hour cellular phone for psychological support, as needed.

8.4.2 Telephone Contact After Dosing Sessions

The goal of the telephone contact is to assess health changes, ensure participant safety, and offer support. The study team will follow-up with the participant by telephone once between Integration Sessions 1.1 and 1.2, 1.2 and 1.3, 2.1 and 2.2, 2.2 and 2.3, 3.1 and 3.2, and 3.2 and 3.3. Each call will last on average 5 to 10 minutes but could be longer to address participant concerns and to adequately assess wellbeing. Additional telephone contact can be initiated at the request of the therapist or participant. If an Integration Session is scheduled on the day of a planned phone contact, the phone contact does not need to be completed.

At each telephone contact, the study clinician will:

- Inquire about any possible changes in health, assess the participant's mental health and the status of any previously recorded AEs, and record AEs as described in Section 9.13.
- Inquire about concomitant medication use.
- Administer the C-SSRS.
- Offer support in accordance with the Treatment Manual.

8.4.3 Integration Sessions

After each Dosing Session, three Integration Sessions will take place. Each session will consist of 90 minutes of therapy. Integration Sessions should not be less than 48 hours apart.

Intervention Cycle 1

- Integration Session 1.1: morning after Dosing Session 1
- Integration Session 1.2: 3 to 14 days after Dosing Session 1
- Integration Session 1.3: 20 to 34 days after Dosing Session 1 and 1 to 7 days in advance of Dosing Session 2. This visit serves two purposes: to continue integration and to prepare for the next Dosing Session. Measures will be administered in accordance with Table 11.

Intervention Cycle 2

- Integration Session 2.1: morning after Dosing Session 2
- Integration Session 2.2: 3 to 14 days after Dosing Session 2

- Integration Session 2.3: 20 to 34 days after Dosing Session 2 and 1 to 7 days in advance of Dosing Session 3. This visit serves two purposes: to continue integration and to prepare for the next Dosing Session. Measures will be administered in accordance with Table 11.

Intervention Cycle 3

- Integration Session 3.1: morning after Dosing Session 3
- Integration Session 3.2: 3 to 14 days after Dosing Session 3
- Integration Session 3.3: 20 to 35 days after Dosing Session 3. This visit will be the final Integration Session prior to entering the follow-up period. Measures will be administered in accordance with Table 11. Discuss safety plan.

During Integration Sessions, the therapist will:

- Record the session.
- Inquire about any possible changes in health. Assess the participant's mental health and the status of any previously recorded AEs. Record AEs as described in Section 9.13.
- Inquire about concomitant medication use and adherence.
- Administer Since Last Visit C-SSRS to assess suicide risk.
- Discuss and review events that occurred with the participant during the Dosing Session, including thoughts, feelings, and memories. If necessary, the therapist will help the participant to reduce any residual psychological distress they are experiencing. The therapist will also encourage the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in Dosing Sessions to emotionally threatening everyday situations. The therapy pairs will be supportive, validate the experience, and facilitate understanding and emotional processing.

Based on clinical judgment due to a participant's time-sensitive clinical need, additional integration sessions will be scheduled to provide additional therapeutic support.

8.5 Follow-up Phase

The Follow-up Phase begins with the Primary Endpoint, includes a follow-up safety call, and ends with the Secondary Endpoint and Study Completion. Once at the Primary Endpoint which is 14±3 weeks after baseline (approximately 1 month after the final Dosing Session), participants will enter into the Follow-up Phase for approximately 2 months until the Secondary Endpoint and Study Completion which are 13±2 weeks (approximately 3 months) after the final Dosing Session (See Figure 1 Study Schema Diagram).

Participants will be encouraged to comply with protocol requirements for concomitant medications and engagement with their primary behavioral providers until the Secondary Endpoint. After the Follow-up Phase, participants will be encouraged to continue care with their primary mental health provider(s) at their home duty station. Every effort will be made to ensure a smooth clinical transition and hand-off from the study therapist to the participant's primary mental health care provider(s).

8.5.1 Primary Endpoint

The Primary Endpoint will occur 14±3 weeks after the CAPS-5-R baseline independent rater session and 1-9 days after $I_{3.3}$. Assessments and data collection will occur as described in Table 13.

8.5.2 Follow-up Safety Call

The study team will call the participant for a safety follow-up phone call 4±1 weeks after the Primary Endpoint to conduct medication reconciliation, assess for AEs, assess for suicidality using the C-SSRS, and conduct other assessments and data collection as described in Table 13.

8.5.3 Secondary Endpoint

The Secondary Endpoint will occur 13±2 weeks after the 3rd Dosing Session. Assessments and data collection will occur as described in Table 13.

8.5.4 Additional Support Sessions During Follow-up Phase

During the Follow-up Phase, the participant will also have access to the study therapist and/or medical provider for brief, problem-focused support if needed via phone or telemedicine. Exceptions may be made to allow for in-person follow-up visits with the study therapist or medical provider on a case-by-case basis based on the participant's clinical need, with an emphasis on a smooth transition of care and hand-off to the participant's primary mental health provider(s) when needed. Datapoints to be recorded include: date, length of session, and type of problem-focused intervention provided. This additional support from the study team will be accessible by the participant if requested until Study Completion, at which point no further research team support will be available.

8.6 Study Completion

8.6.1 Visit Procedures and Definition

Study Completion will take place 0-7 days after Secondary Endpoint, approximately 2 months after the Primary Endpoint (i.e., 13±2 weeks after the final Dosing Session). Participants who have withdrawn from dosing but have continued for follow-up will also complete the Study Completion procedures per protocol after the Secondary Endpoint.

At the Study Completion Visit, the Study Team will:

- Inquire about any possible changes in health. Assess the participant's mental health and the status of any previously recorded AEs. Record AEs as described in Section 9.13.
- Inquire about concomitant medication use and adherence.
- Administer Since Last Visit C-SSRS.
- Provide and discuss the Study Exit Plan.
- Review potential timeline until study unblinding upon study database lock and how they will be informed at that time.
- Actively support participant in completion of outcome measures per protocol.

After all Study Completion procedures are completed, the participant is considered terminated from the study, and the participant may discontinue any requirements related to the study. The study team will provide a Study Exit Plan, which may include a referral for additional medical or therapeutic care, as described in Section 8.6.2 Study Exit Plan.

8.6.2 Study Exit Plan

At Study Completion, participants will be provided with a Study Exit Plan. This Study Exit Plan summarize treatments completed, current medications, how they will be informed of unblinding, and contact information for more information about the study if needed. Participants may request or be offered a referral for further mental health or medical care if appropriate. Enrolled participants who withdraw from the study early will be provided a Study Exit Plan at their last contact. Screen Failures will be provided a referral if requested.

9 Eligibility, Efficacy, and Safety Assessments

See Table 5 Timeline of Study Measures for a full schedule of administered assessments.

9.1 Primary Outcome Measure: CAPS-5-R

The Revised Clinician-Administered PTSD Scale for DSM-5 (CAPS-5-R) is a newly developed and recently released version of the CAPS-5 which is considered the gold standard in PTSD assessment and is used broadly both in clinical and research contexts. The CAPS-5-R improves upon the CAPS-5 by incorporating feedback from a wide variety of raters over the past decade. The goals of the CAPS-5-R were to "(a) increase the standardization of administration and scoring, (b) improve the quality of the information obtained, (c) expand the rating scale to capture more variability in severity scores, (d) make it easier to learn, and (e) maintain backward compatibility with the CAPS-5."[190] To clarify the last point, CAPS-5 scores are embedded in the CAPS-5-R. Although the psychometrics of the CAPS-5-R have been validated, appropriate cutoffs have yet to be determined until more studies are conducted using the CAPS-5-R. For these reasons, our study will use severity cutoffs using CAPS-5 instead of CAPS-5-R scores. We intend to report scores for both the CAPS-5 and CAPS-5-R.[190,191]

The CAPS-5 is a 30-item structured interview that has been validated across several populations including the military. In addition to assessing the 20 DSM-5 PTSD symptoms, questions target the onset and duration of symptoms, subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype.[192]

9.1.1 Independent Rater CAPS-5-R Assessments

Independent raters will be utilized to collect the CAPS-5-R at Baseline, Primary Endpoint, and Secondary Endpoint. Independent raters will be composed of appropriately trained and supervised staff. Independent raters will be composed of supervised clinical psychology practicum students (PhD and PsyD Candidates) or independent licensed clinical psychologists that are proficient in administering the CAPS-5-R. They will be trained and supervised to maintain scoring accuracy and following the program double scoring and consensus rating process. Independent raters will also participate in group supervision to address scoring

discrepancies and to participate in ongoing education to uphold fidelity to the standard administration procedures of the CAPS-5-R.

For this study, the independent rater assessment team will administer approximately 273 CAPS-5-Rs, with each assessment taking about one hour. In addition to the administration of these assessments, the team will allocate time for training, supervision, double scoring, and addressing any scoring discrepancies.

9.1.2 Training and Supervision for CAPS-5-R Independent Raters

All independent raters will have completed comprehensive and rigorous training, including didactic sessions on PTSD and the CAPS-5-R, as well as a multi-stage VA CAPS-5-R Clinician Training, which emphasizes scoring consistency and reliability. Following didactic training, independent raters participate in mock interviews and rate CAPS-5-R assessments until they establish strong Interrater Reliability (IRR). Independent raters will engage in weekly group supervision and consensus meetings will be held to review discrepant cases to ensure scoring standards are aligned.

9.1.3 Reliability: Assessment Administration and Double Scoring of CAPS-5-R

Independent raters will follow a rigorous double scoring process to ensure precision in administering the CAPS-5-R. Each assessment is assigned a primary assessor/rater and a double scorer, with assessments either live-double scored or video-double scored shortly after the assessment, depending on assessor availability. Any score discrepancies are reviewed in group supervision with a licensed clinical psychologist to reach consensus. This process, supported by regular feedback, consensus meetings, and ongoing training, ensures the highest standards in CAPS-5-R scoring and administration.

9.2 Secondary Outcome Measures

9.2.1 Durability of CAPS-5-R between Primary and Secondary Endpoints

As described in Section 9.1, the CAPS-5-R will serve as the primary outcome measure for this study. A secondary outcome measure will be the difference in CAPS-5-R scores between the Primary Endpoint Visit and the Secondary Endpoint Visit. The CAPS-5-R will be administered at both the Primary Endpoint Visit, which will occur one month after the third Dosing Session, as well as the Secondary Endpoint Visit, which will occur three months after the third Dosing Session. We will examine the differences in CAPS-5-R scores between the Primary and Secondary Endpoints to evaluate the durability of the treatment effect.

9.2.2 WHO Disability Assessment Schedule 2.0 (WHODAS 2.0)

WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) is a generic assessment instrument for health and disability across all diseases, including mental, neurological, and addictive disorders and is easy to administer (5 to 20 minutes). WHODAS 2.0 produces domain-specific scores for six different functioning domains – cognition, mobility, self-care, getting along, life activities and participation.[193] Differences in WHODAS 2.0 scores between the Primary and Secondary Endpoints will also be examined to evaluate the durability of effect.

9.2.3 Overlapping Support Events

A secondary outcome measure of this study will be the frequency of simultaneously overlapping Support Events per study arm and combined overall. Support Events are defined as instances when a study team member who is not the primary therapist enters a dosing room to provide assistance. Further details about Support Events can be found in Section 6.3.3. Our study will collect data on study-specific Support Event reporting forms for each instance that a study team member provides in-person assistance to a dosing room. All of the data elements collected on the Support Event reporting forms can be found in Section 6.3.5.

9.3 Screening Measures

9.3.1 Life Events Checklist for DSM-5 (LEC-5)

The Life Events Checklist for DSM-5 (LEC-5) is a self-report measure designed to screen for potentially traumatic events in a respondent's lifetime. The LEC-5 assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items.[194] In addition to being a screening measure, the LEC-5 will also be used as an exploratory measure collected throughout the study before each administration of the PCL-5.

9.3.2 PTSD Checklist for DSM-5 (PCL-5) (after LEC-5)

PTSD Checklist for DSM-5 (PCL-5) is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. The PCL-5 is a self-report measure that can be completed by patients in a waiting room prior to a session or by participants as part of a research study. It takes approximately 5-10 minutes to complete. A PCL-5 cutoff score between 31-33 is indicative of probable PTSD across samples. Our study will use a cutoff of 38 for eligibility, indicating at least moderate PTSD. Five points is a minimum threshold for determining whether an individual has responded to treatment, and 10 points is a minimum threshold for determining whether the improvement is clinically meaningful.[195,196] In addition to being a screening measure, the PCL-5 will be used as an exploratory outcome measure of PTSD severity throughout the study approximately 3-5 weeks after each Dosing Session.

9.3.3 Columbia Suicide Severity Rating Scale (C-SSRS)

Columbia Suicide Severity Rating Scale (C-SSRS) (Lifetime and Last Month) will be used at Screening to determine worst ever suicidality across the individual’s lifetime as well as over the past month. C-SSRS is a metric used to distinguish the domains of suicidal ideation and suicidal behavior. It consists of 4 constructs: severity of ideation, intensity of suicidal ideation, a behavior scale, and a lethality scale. The C-SSRS subscales and total suicidal ideation score (2-25) have been found to have reasonable convergent and divergent validity with other suicidal ideation and behavior scales (Columbia Suicide History Form, the Montgomery-Asberg Depression Rating Scale, and the Beck Depression Inventory) and high sensitivity and specificity for suicidal behavior classification when compared with another behavior scale and an independent suicide evaluation board. The C-SSRS is open source and available online in its most updated form.[197-199] See Exclusion Criteria (Section 5.2) for thresholds for exclusion based on C-SSRS responses.

9.3.4 Structured Clinical Interview for DSM-5 Screening Personality Questionnaire (SCID-5-SPQ)

Structured Clinical Interview for DSM-5 Screening Personality Questionnaire (SCID-5-SPQ) is a 106-item self-report questionnaire designed to screen for possible PD. Items correspond with the questions in the interview version probing all symptoms of 10 DSM-5 PDs and are rated with "yes" or "no."[200] The SCID-5-SPQ will only be used for eligibility screening but will not be used at any other point throughout the study.

9.3.5 Structured Clinical Interview for DSM-5 for Personality Disorders (SCID-5-PD)

Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD) is a semi-structured diagnostic interview for clinicians and researchers to assess the 10 DSM-5 Personality Disorders across Clusters A, B, and C as well as Other Specified Personality Disorder. Diagnosis can be reported categorically (quantitative) or dimensionally (qualitative).[200] The SCID-5-PD will only be used for eligibility screening for personality disorders that screened positive on the SCID-5-SPQ, but it will not be used at any other point throughout the study.

9.3.6 Mini-International Neuropsychiatric Interview (MINI)

Mini International Neuropsychiatric Interview (MINI) was designed as a brief structured diagnostic interview for the major psychiatric disorders and takes roughly 15 minutes to administer. MINI assesses the 17 most common disorders in mental health. Disorders were selected based on current prevalence rates of 0.5% or higher in the general population in epidemiology studies.[201] The MINI will only be used for eligibility screening to determine psychiatric comorbidities and determine PTSD diagnosis, but it will not be used at any other point throughout the study.

9.4 Exploratory Measures

9.4.1 Columbia Suicide Severity Rating Scale (C-SSRS)

Columbia Suicide Severity Rating Scale (C-SSRS) (Last Month and Since Last Visit) will be used to determine potential changes in suicidality throughout the course of the study. Note: Lifetime and Last Month versions are used at screening; whereas, the Last Month version is used once more at the first Preparation Session, and the Since List Visit version is used throughout the rest of the study. C-SSRS is a metric used to distinguish the domains of suicidal ideation and suicidal behavior. It consists of 4 constructs: severity of ideation, intensity of suicidal ideation, a behavior scale, and a lethality scale. The C-SSRS subscales and total suicidal ideation score (2-25) have been found to have reasonable convergent and divergent validity with other suicidal ideation and behavior scales (Columbia Suicide History Form, the Montgomery-Asberg Depression Rating Scale, and the Beck Depression Inventory) and high sensitivity and specificity for suicidal behavior classification when compared with another behavior scale and an independent suicide evaluation board. The C-SSRS is open source and available online in its most updated form.[197-199]

9.4.2 Medical Profile Status Questionnaire (MPSQ)

The Medical Profile Status Questionnaire (MPSQ) is an 8-item self-report measure developed for this protocol to characterize participants' military medical duty status and fitness for duty over time. The MPSQ assesses: (1) current military medical duty status, categorized as full duty/no restrictions, temporary restrictions (e.g., temporary profile, LIMDU, light duty), permanent restrictions (e.g., permanent profile, permanent LIMDU), or medical separation/retirement; (2) the type of condition associated with any duty restriction (PTSD, other mental health condition, non-mental health condition); (3) the date of onset of the current restriction; (4) the approved duration of the restriction; (5) any changes in duty restriction status over the preceding month (e.g., restriction ended, became more or less limiting, was extended, or a new restriction began); (6) whether the participant believes something related to the study contributed to any such change; (7) a free-text description of perceived study contribution, if applicable; and (8) whether the participant has been referred for, is currently undergoing, or has completed a medical board or disability evaluation process. The MPSQ is collected during screening and approximately monthly until secondary endpoint. Between-group differences in changes in medical profile status will be evaluated to characterize the impact of the study intervention on fitness for duty.

9.4.3 Drug Use Desire and Intent Questionnaire (DUDIQ)

The Drug Use Desire and Intent Questionnaire (DUDIQ) is a two-item measure developed for this protocol to assess participants' hypothetical desire and intention to use MDMA outside of a medical or therapeutic context. Items are rated on a 0–100 visual analog scale (VAS) and include: (1) desire to take MDMA in the future, and (2) likelihood of taking MDMA in the future. These items parallel constructs used in human abuse potential research, where "wanting" and "willingness" to take a drug again provide distinct but complementary information about reinforcement liability.[202] The DUDIQ allows for systematic assessment of participants' interest in future nonmedical use, providing data directly relevant to FDA expectations for abuse potential evaluation.

9.4.4 Psychedelic Preparedness Scale (PPS)

Psychedelic Preparedness Scale (PPS) is an effective prospective as well as retrospective tool for measuring preparedness and estimating responses to psychedelics exposure. PPS demonstrated good reliability and validity and was able to predict both acute and post-acute psychological effects induced by psychedelics. Significant differences between those scoring high and low (on psychedelic preparedness) before the psychedelic experience were found on measures of mental health/wellbeing outcomes assessed after the experience, suggesting that the scale has predictive utility.[203]

9.4.5 Beck Depression Inventory-II (BDI-II)

Beck Depression Inventory-II (BDI-II) is a 21-item self-report inventory to assess symptoms and severity of depression. It has been widely used in research and clinical practice with well-established psychometric properties. Items are summed to create a total score, with higher scores indicating higher levels of depression.[204]

9.4.6 Pittsburgh Sleep Quality Index (PSQI)

Pittsburgh Sleep Quality Index (PSQI) is a widely used self-report questionnaire that assesses sleep quality over a one-month time interval. Component scores of the PSQI range from 0 to 3, with 3 indicating the greatest dysfunction or disturbance. The seven component scores are then summed to obtain a global PSQI score, which ranges from 0 to 21. Higher scores indicate poorer sleep quality, with a score greater than 5 suggesting significant sleep difficulties.[205,206]

9.4.7 Pain, Enjoyment of Life and General Activity Scale (PEG)

The Pain, Enjoyment of Life and General Activity Scale (PEG) is a 3-item brief self-report pain outcome measure that assesses pain intensity and functional interference regarding enjoyment of life and general activity. Item scores range from 0-10 and the measure is scored by averaging the items. It has demonstrated good reliability, validity, and responsiveness to treatment in samples of patients with chronic pain.[207]

9.4.8 The Blast Exposure Threshold Survey (BETS)

The Blast Exposure Threshold Survey (BETS) is a recently developed self-report measure of lifetime blast exposure. The questions assess 5 types of weapon systems and ask about years over a lifetime, months per year, days per month, rounds or explosions per day, and frequency of back-to-back days of exposure. The survey typically takes about 15 minutes to complete, but the time may vary. The results can be used to compute a quantitative generalized blast exposure value, which has been shown to correlate with blast-related symptom severity.[208] Many Service Members have had significant lifetime blast exposure, but it is unknown whether the experimental interventions in this research study will differentially affect service members with greater or lesser history of blast exposure.[209]

9.4.9 The Headache Impact Test 6 (HIT6)

The Headache Impact Test 6 (HIT6) is a standard self-report questionnaire that is commonly used to assess the burden of headaches in traumatic brain injury (TBI) patients and others with headache disorders. It takes less than 5 minutes to complete on paper or on a computer system. Headache disorders are especially common in military service members with TBI.[210] Changes in HIT6 over time may be expected to be sensitive to either improvements or worsening/adverse effects on headaches due to the interventions performed in the research study.

9.4.10 The NIH Toolbox

The NIH Toolbox is another standard cognitive performance assessment battery that has been used for many diseases and conditions around the world.[211] A typical test battery takes about 25 minutes to complete on a standardized tablet computer.[212] Individual tests assess attention, processing speed, procedural memory, visual memory, and thinking ability. There are well publicized norms for people with a wide range of age and educational attainment.[211,213,214] It is expected to be sensitive to either improvements or worsening/adverse effects on cognitive performance due to the interventions performed in the research study.

9.4.11 Moral Injury Outcome Scale (MIOS)

Moral Injury Outcome Scale (MIOS) is a 14-item scale designed to capture the severity of moral injury outcomes in response to an index event. It contains two factors: Shame-Related (SR) and Trust-Violation-Related Outcomes and has been found to have reliability and convergent validity.[215]

9.4.12 Multidimensional Psychological Flexibility Inventory-24 (MPFI-24)

Multidimensional Psychological Flexibility Inventory-24 (MPFI-24) is a comprehensive assessment of psychological flexibility. This questionnaire consists of 24-items answered on a 0 (“Never True) to 5 (“Always True”) scale and comprises 12 subscales reflecting two global dimensions: six subscales reflecting psychological flexibility (present moment awareness, cognitive diffusion, acceptance, self-as-context, values and committed action) and six subscales reflecting psychological inflexibility (lack of contact with the present moment, cognitive fusion, experiential avoidance, self-as-content, lack of contact with values and inaction). Confirmatory factor analysis demonstrated excellent model fit, and the MPFI-24 has good construct validity, as well as good convergent and divergent validity.[216,217] Further, in a recent review of psychological flexibility measures, the MPFI-24 was selected as a preferred measure for its comprehensiveness and for being empirically distinct from negative affect and distress.[218]

9.4.13 Adverse Childhood Experience Questionnaire (ACE)

The Adverse Childhood Experience Questionnaire (ACE) is a brief rating scale designed and first published by Felitti et al. The ACE has provided substantial epidemiological evidence concerning the link between adverse childhood experiences and adult mental and physical illnesses. Since its introduction in 1998, the ACE has been used in research to assess a diverse set of subpopulations throughout the United States, Europe, and Asia. Validation studies suggest that ACE scoring remains strong as a predictive measure despite potential distortion due to historical self-reporting-memory artifacts.[219]

9.4.14 Multidimensional Scale of Perceived Social Support (MSPSS)

The Multidimensional Scale of Perceived Social Support (MSPSS) is a 12-item questionnaire to identify an individual’s perceived level of social support with family, friends, and significant others.[220] MSPSS has been shown to have good internal and test-retest reliability, as well as good validity.[220,221]

9.4.15 Interpersonal Needs Questionnaire (INQ-15)

The 15-item Interpersonal Needs Questionnaire (INQ-15) will be used to assess two proximal interpersonal risk factors for suicidal ideation and behavior: perceived burdensomeness (e.g., “I feel like a burden on others”) and thwarted belongingness (e.g., “I feel disconnected from others”). Participants rate each item on a 7-point Likert scale (1 = Not at all true for me to 7 = Very true for me). The INQ-15 has demonstrated good psychometric properties across multiple studies.[222,223]

9.4.16 Perceived Invalidation of Emotion Scales (PIES)

Perceived Invalidation of Emotion Scale (PIES) is a validated 10-item screen to measure perceived emotion invalidation. Emotion invalidation is an interaction perceived by the individual as implying that their emotions or affective experiences are incorrect or inappropriate. PIES prioritizes the perception of the individual sharer over the intent or objective behavior of the respondent.[224]

9.4.17 Health and Work Health and Work Performance Absenteeism and Presenteeism Short Form (HPQ-SF)

Health and Work Performance Questionnaire Short Form (HPQ-SF) is extracted from the larger HPQ and contains the questions that are needed to quantify the burden of absenteeism and presenteeism.[225]

9.4.18 WHO Quality of Life-BREF (WHOQOL-BREF)

WHO Quality of Life-BREF (WHOQOL-BREF) is a 26-item instrument consisting of four domains: physical health (7 items), psychological health (6 items), social relationships (3 items), and environmental health (8 items); it also contains QOL and general health items. WHOQOL-BREF domain scores demonstrated good discriminant validity, content validity, internal consistency, and test–retest reliability.[226]

9.4.19 Stanford Expectations of Treatment Scale (SETS)

The Stanford Expectations of Treatment Scale (SETS) is a tool for measuring treatment expectancy. The six items of the SETS contain two subscales to measure positive expectancy and negative expectancy. Factor analysis results indicate that the items load onto two distinct factors of positive and negative expectancy. Most participants complete the SETS in approximately one minute and the measure has been found to demonstrate strong internal reliability and predictive validity.[227]

9.4.20 Alcohol Use Disorders Identification Test (AUDIT)

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems. A score of 8 or more is considered to indicate hazardous or harmful alcohol use.[228-230]

9.4.21 Drug Use Disorders Identification Test (DUDIT)

Drug Use Disorders Identification Test (DUDIT) is an 11-item self-administered screening instrument for drug-related problems, giving information on the level of drug intake and selected criteria for substance abuse/harmful use and dependence.[231]

9.4.22 The Timeline Followback (TLFB) Assessment Method to Assess Alcohol Use

The Timeline Followback (TLFB) Assessment Method to Assess Alcohol Use employs a calendar format designed to retrospectively assess daily alcohol consumption. It has been

recognized by the World Health Organization and the FDA as the gold standard for measuring alcohol consumption in clinical trials. The measure is self-report via written response and takes about 5-10 minutes to complete. For measuring alcoholic beverages, the TLFB has patients quantitatively record the amount of alcoholic beverages consumed for every day of a specified interval (e.g., 30 days, since the date of the last assessment). When reporting the amount of alcohol consumed, the patients use a standard drink metric. The TLFB gives a continuous picture of a patient's alcohol use in order to generate alcohol-related outcome variables (e.g., percent heavy drinking days, drinks per drinking day, abstinence).[232,233]

9.4.23 Smoking and Tobacco use Questionnaire (STUQ)

Smoking and Tobacco Use Questionnaire (STUQ) asks participants for the number of days and the amount per day that they smoke combustible cigarettes.[234] They will also be asked the number of days and number of sessions per day that they use electronic cigarettes containing nicotine. Finally, they will be asked the number of days that they use chewing tobacco, snuff, dip, snus, or dissolvable tobacco products, such as Copenhagen, Grizzly, Skoal, or Camel Snus. Baseline will ask about use over the past 30 days whereas follow-up will ask about use over the past seven days. The outcomes will include seven-day point prevalence abstinence and change in quantity and proportion of days of use.

9.4.24 Drug Use Questionnaire

The Drug Use Questionnaire asks participants to report on the number of occasions of use of an array of commonly used psychoactive drugs. These include both illicit and prescribed drugs that are used in a non-prescribed way. Number of drug use occasions is separated into 9 response options (0, 1, 2, 3, 4-5, 6-9, 10-19, 20-39, and 40 or more occasions). The Baseline version asks about lifetime, past year, and past 30 day use. The Follow-up and Long-term Follow-up versions ask about use since the last time of assessment. This questionnaire was adapted from the Monitoring the Future study measure that is publicly available on PhenX (https://www.phenxtoolkit.org/protocols/view/510303).[235,236]

9.4.25 Working Alliance Inventory-Short Revised (WAI-SR)

The Working Alliance Inventory-Short Revised (WAI-SR) is a 12-item questionnaire to assess three aspects of the therapeutic alliance: agreement on the tasks of therapy; agreement on the goals of therapy; and the development of an affective bond. The WAI has been widely used in research and clinical practice as a method for assessing therapeutic relationships and has been found to have convergent validity with other measures of therapeutic alliance.[237]

9.4.26 Modified Drug Effects Questionnaire–3 (mDEQ-3)

The Modified Drug Effects Questionnaire–3 (mDEQ-3) is a three-item adaptation of the widely used Drug Effects Questionnaire (DEQ), a validated instrument for assessing subjective drug effects in human abuse liability studies.[238] The mDEQ-3 retains the two core DEQ constructs most relevant for reinforcement— (1) retrospective drug liking and (2) retrospective desire for more of the drug—and adds a third item assessing euphoria. The inclusion of euphoria follows FDA guidance on abuse potential assessment, which recommends evaluation of euphoria as an abuse-related effect in addition to drug liking and "take again" measures.[239]

All items are rated on a 0–100 VAS. In this study, the mDEQ-3 is administered the morning after each dosing session to capture participants' retrospective appraisal of the acute drug effects, while minimizing conflation with psychotherapy content. These data provide structured evidence regarding the reinforcing and hedonic properties of MDMA, directly addressing FDA expectations for abuse liability evaluation.

9.4.27 Euphoria Assessment Pre-Dosing (EA-Pre) and Post-Dosing (EA-Post)

The Euphoria Assessment Pre-Dosing (EA-Pre) and Post-Dosing (EA-Post) is a three-item measure developed for this protocol to assess participants' experience of euphoria prior to and following MDMA administration. The inclusion of euphoria assessments follows FDA guidance on abuse potential assessment, which recommends evaluation of euphoria as an abuse-related effect in addition to drug liking and "take again" measures.[239] All items are rated on a 0–100 VAS and include: (1) one pre-dosing item to assess current experience of euphoria, and (2) two post-dosing items to assess current experience of euphoria and peak euphoria experienced during MDMA administration. These data provide structured evidence regarding the reinforcing and hedonic properties of MDMA, directly addressing FDA expectations for abuse liability evaluation.

9.4.28 Blinding Survey

Blinding Survey is a brief, self-report rating questionnaire designed for this study to evaluate whether participants were effectively blinded to which treatment they received during the experimental procedure. This survey was designed for the current study to in part address FDA Advisory Committee concerns of functional unblinding in previous studies of MDMA-AT for PTSD.[240,241] The survey asks participants which treatment they believe they received, with the percentage of correct or incorrect responses indicating the extent to which they were blinded. Furthermore, participants are asked to rate their confidence level and to indicate if communication with other participants influenced their answers. The survey will also assess therapist confidence regarding their ability to determine MDMA or placebo dosing and if changes to their perceived accuracy is due to ongoing participation in this study. This measure would contribute to the evaluation of low-dose MDMA as an active control that is effective at mitigating functional unblinding.

9.4.29 Qualitative Interview

A qualitative interview developed by the research team will be completed at the primary endpoint to obtain participant feedback regarding their experience in the study and its impacts. The qualitative interview will be conducted by study staff at the primary endpoint or, when possible, at the conclusion of a participant's enrollment in the study (i.e., withdrawal or early termination). The qualitative interview will include questions eliciting participants' feedback for quality/process improvement as well as reported changes in clinical, social, and occupational outcomes. Participant narrative responses to the open interview questions will be recorded, thematically coded, assessed for quality/process improvement recommendations, and included in exploratory analyses.

9.4.30 Endorsed and Anticipated Stigma Inventory: Beliefs About Mental Health Treatment

The Endorsed and Anticipated Stigma inventory (EASI) is a 40-item self-report inventory that consists of 5 scales assessing mental health beliefs regarding willingness to seek mental health treatment. This study will utilize the Beliefs About Mental Health Treatment scale of the EASI to assess endorsed stigma by participants regarding seeking mental health services. The Beliefs About Mental Health Treatment scale is composed of only 8 items out of the 40 total items and utilizes a 5-point Likert-type response format.[242] The EASI was designed to assess dimensions of stigma-related beliefs among military and veteran populations. The EASI has been found to have good content validity, internal consistency, and discriminative validity.[242]

9.4.31 Ohio State University Traumatic Brain Injury (OSU-TBI) Inventory

The Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) is a structured interview designed to assess an individual's lifetime history of traumatic brain injuries (TBIs).[243] This study will utilize the OSU TBI-ID to screen participants for prior TBIs before enrollment, ensuring that brain injury history is considered in our analysis. The method screens for injury and gathers information to determine if TBI diagnostic threshold is met (loss of consciousness, feeling dazed or confused, memory gaps), TBI severity, as well as capturing periods of time where multiple head impacts or exposures may have occurred.[243] This tool has been validated in multiple studies, showing strong inter-rater and test-retest reliability, as well as predictive validity through its association with various measures, including cognitive performance.[244]

9.4.32 Confusion Assessment Method (CAM)

The Confusion Assessment Method (CAM) is a well validated and widely used clinician-administered assessment of confusion. It is most often used for assistance in diagnosis of delirium in inpatient settings, but it can be clinically useful in other settings. The CAM has 9 questions (several have sub questions) that capture several domains of mental status to include acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation and retardation, and altered sleep-wake cycle.[245] In the context of our study, the CAM is modified to exclude the final question on sleep-wake cycle due to its irrelevance for determining appropriateness to discharge at the end of each Dosing Session; all other aspects of the modified CAM are identical to the original CAM.

The modified Confusion Assessment Method CAM will be administered twice for each Dosing Session. The first administration will be prior to dosing and is only used to establish a baseline to compare post-dosing. The second administration will be at the conclusion of the Dosing Session to determine safety to discharge. At the end of the Dosing Session, if all questions are negative or return to their pre-dosing baseline, the participant will be determined to be safe to discharge after completing all other post-dosing procedures. If any questions are positive on the post-dosing CAM that were not positive on the pre-dosing CAM, the CAM will be readministered every 10 minutes until all questions are negative or return to pre-dosing baseline. Any positive findings will be reported to the study physician for determination of clinically appropriate actions and disposition.

9.4.33 Reactions to Touch Measure (RTM)

The Reactions to Touch Measure (RTM) is a 20-item self-report scale to assess participant reactions to any physical touch between therapist and participant that occurs during the psychedelic sessions. The measure examines location of touch, subjective intensity of touch, and perceived effects of touch.[246]

9.4.34 Self–Compassion Scale-Short Form (SCS-SF)

The Self-Compassion Scale-Short Form (SCS-SF) is a 12-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion and recognizing one's own flaws and suffering as part of common human experience.[247] Because the measure is being administered repeatedly and we wanted it to be sensitive to change, we modified the measure slightly from the original to refer only to experiences in the last week. It is estimated to take about 3 minutes to complete. This brief measure has been shown to correlate highly with the well-validated longer version of this scale and to have excellent psychometric characteristics itself.[247]

9.4.35 Acceptability: Theoretical Framework for Acceptability (TFA)

Theoretical Framework of Acceptability (TFA) was developed to assess the acceptability of the design, evaluation, and implementation of a healthcare intervention. The TFA consists of seven components (affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy). The 7-items of TFA are computed to determine total mean general acceptability of the intervention.[248]

9.4.36 Tolerability: Dropout Rate for Local and Non-Local Participants

Dropout rates (tolerability) and reasons for dropout will be evaluated for both local and non-local participants not only to determine overall tolerability but also to describe potential group differences in local vs non-local participants. A < 20% dropout rate for reasons related to the study intervention among local and non-local participants will be operationalized to indicate that the treatment is tolerable.

9.5 Psychiatric Safety

9.5.1 Suicidal Ideation and Behavior Risk Monitoring

The study team will minimize risk of suicidality by monitoring all participants longitudinally with the C-SSRS at screening, baseline, and each preparation/dosing/integration session for presence and severity of suicidal ideation and/or behavior (see Table 10, Table 11, and Table 12 for all C-SSRS timepoints throughout the study).

In addition, participants will be regularly asked about access to lethal means by study clinicians. Possible mitigation of access to lethal means will be discussed at baseline and participants will be encouraged to implement mitigation strategies (trigger locks, excess medication disposal, etc.). Any emergence or changes to suicidality will be evaluated by the participant's study therapist and safety procedures implemented as detailed below.

Participants with a history of suicide attempts will not be excluded unless significant risk of suicidal ideation and/or behavior is detected, per Exclusion Criteria described in Section 5.2 and based on the clinical judgment of the PI, study team, and Independent Safety Monitor.

A qualified study team member will administer the C-SSRS at timepoints detailed in Table 10, Table 11, and Table 12, and as needed depending on clinical presentation of the participants to monitor for development and intensity of suicidal ideation and/or behavior. The study team will implement the following plan to assess for elevated or imminent suicide risk.

1. If the participant has current suicidal ideation, but no specific plan to commit suicide (Suicidal Ideation Score=4), the individual administering the C-SSRS will ensure:
    a. The participant is evaluated by the investigator and/or site physician to determine an appropriate course of action. Findings will be discussed with the participant and their personal therapist, if applicable.
    b. A standardized written safety plan will be developed with a copy being given to the participant and one being uploaded into their medical record. The Lead Monitor will review the safety plan with participants at Integration Session 3.3.
    c. Regular check-ins via phone or in-person will be continued until the participant has stabilized or a new course of action is taken based on changes in C-SSRS score and/or ongoing clinical assessment.
    d. Notification of the sponsor within 24 hours of this event and provide a narrative for the AE for expedited reporting to FDA, ORA, and drug manufacturer. Increases in suicidality will be captured as an AESI per Section 9.13.5 and evaluated for seriousness. SAEs will be reported per regulatory guidance.
    e. Treatment would be continued when deemed appropriate by the investigator and Independent Safety Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up.
2. If the participant has suicidal ideation, and a plan to complete suicide (Suicidal Ideation Score=5) or positive Suicidal Behavior (Score greater than or equal to 1), the individual administering the C-SSRS will assess whether the risk is imminent. A Suicidal Ideation score of five does not necessarily indicate an immediate risk if the thoughts are fleeting, fairly easily controlled, and protective factors deterrents are strong. If there is no imminent risk, the individual will follow the procedure described above. If there is imminent risk of suicidal behavior, the individual will ensure:
    a. Participants are evaluated by the investigator or site physician to determine an appropriate course of action, and the therapy team may contact their personal therapist, who will be invited to come to the study site to assist, depending on their location.
    b. If it is determined that the participant is at imminent risk of suicide, the therapy team will do one of the following:
        i. Escort the participant to the ED (Emergency Department) if the imminent suicide risk is recognized during an in-person evaluation. If the participant is currently located near the study site when the imminent risk of suicide is first recognized by the study team, the study team will alert the predetermined emergency contact, the participant's command, and/or local Emergency Medical Services (EMS) services.
        ii. Escort the participant to an appropriate mental health services facility (e.g., hospital psychiatric unit); or

iii. Call EMS and ensure that the participant is transferred to the responding medical personnel.

c. If the participant will not comply and wishes to leave without consultation, call EMS. Explain that the participant is in immediate danger of committing suicide. Provide a complete description of the participant and give any other needed details to ensure the participant's safety.
d. Notification of appropriate members of the study team and sponsor representatives within 24 hours, provide a narrative for the AE for expedited reporting to FDA.
e. The event will be collected as an AESI per Section 9.13.5 and seriousness will be evaluated. SAEs will be reported per regulatory guidance.
f. Treatment would be continued when deemed appropriate by the investigator and Independent Safety Monitor, unless it is determined that treatment should be discontinued, in which case the participant will enter follow-up.

9.5.2 Anxiety or Psychological Distress

Anxiety or psychological distress during the study may occur during or after Dosing Sessions. Several layers of measures are implemented to ensure participants are afforded the support they need to manage any anxiety or distress that may emerge. These measures include:

- Excluding individuals who may be more vulnerable (e.g., individuals diagnosed with psychotic spectrum disorders)
- Preparation Sessions that include discussions of what to expect during the Dosing Session and practicing emotional regulations strategies
- Establishing therapeutic rapport and trust between the participant and therapist
- Close monitoring and immediate availability by the therapist and study team for support during Dosing Sessions
- Integration Sessions to therapeutically process any anxiety or distress
- Phone contacts between Integration Sessions

During the Preparation Sessions, participants will be made aware of the fact that difficult emotions, including grief, rage, fear, or panic, may arise during Dosing Sessions. The therapist will make every effort to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of each Dosing Session, including empathic listening on the part of the therapist and implementation of emotional regulation strategies.

Anxiety or psychological distress due to MDMA administration may arise as early as initial onset of MDMA physiological or subjective effects (approximately 30 minutes after administration) and may occur periodically at times throughout a Dosing Session until the MDMA's effects have dissipated. Anxiety or psychological distress during a Dosing Session may last for as short as several seconds or for as long as the duration of the session. Severity of the anxiety or psychological distress may range from mild and self-limited, to requiring reassurance and therapeutic support by the therapist, to in rare cases requiring pharmacotherapeutic support (specifically, lorazepam) prescribed by the study physician to adequately manage adverse effects (see Section 6.7.3 Permitted Concomitant Medications).

If a participant remains severely anxious, distressed, or otherwise psychologically unstable after the conclusion of a Dosing Session, the therapist, physician, or another clinical study staff will

remain with the participant to employ emotional regulation techniques, help them further process their experience, and if needed, implement de-escalation strategies, until either:

1. Their symptoms resolve completely or improve to a self-manageable level (residual symptoms will be addressed during follow-up Integration Sessions and/or phone calls with their study therapist),
2. They are transferred to the Emergency Department (ED) as soon as possible as clinically indicated, or
3. If combative or violent, a Code Gray is called immediately.

During this post-dosing stabilization period, the study physician may also prescribe an appropriate medication to address the specific adverse effects in question (e.g., lorazepam for severe anxiety or zolpidem for anticipated insomnia) (see Section 6.7.3 Permitted Concomitant Medications).

A participant's outpatient therapist and/or psychiatrist (if they have one) should be engaged by the study team and involved in the management of any ongoing psychiatric adverse effects.

9.5.3 Illicit or Non-prescribed Substance Use

The use of illicit or non-prescribed substances during study participation poses significant safety risks due to potential pharmacological interactions with the MDMA, compromises the scientific integrity of study data, and is inconsistent with eligibility requirements and the Uniform Code of Military Justice (UCMJ). Accordingly, any confirmed illicit or non-prescribed substance use constitutes a non-modifiable criterion for withdrawal from thet study.

Detection Methods

Non-prescribed illicit substance use may be identified through either of the following:

- Objective detection: A qualitative urine drug screen (UDS) or point-of-care (POC) drug screen collected at any study visit that is confirmed positive for a non-prescribed substance and cannot be better explained as a false positive due to a concomitant prescribed medication or documented dietary practice. The standard screening panel includes amphetamines, barbiturates, cocaine, methadone, opiates, oxycodone, fentanyl, phencyclidine (PCP), cannabinoids, and benzodiazepines.
- Subjective report: Self-reported use of any non-prescribed illicit substance disclosed during clinical interviews, concomitant medication reconciliation, administration of study measures (e.g., TLFB, DUDIT, DUQ, STUQ), or any other study contact.

Stopping Criteria

If illicit or non-prescribed substance use is objectively detected or subjectively reported at any point following enrollment, the following stopping criteria apply:

1. Immediate suspension of study intervention. The participant will not receive any further doses of investigational product. If the finding occurs prior to a scheduled Dosing Session, the session will not proceed. If the finding occurs during an active Dosing Session, no supplemental dose will be administered.
2. Study termination. The participant will be terminated from the study as follows:
    - If the finding occurs prior to randomization and the first Dosing Session, the participant will be classified as a Pre-randomization Early Termination (see Section 7.3.1).

- If the finding occurs after randomization and receipt of investigational product, the participant will be classified as a Post-randomization Early Termination (see Section 7.3.2.1). The participant will be considered evaluable and included in intent-to-treat and safety analyses. The participant will be invited to complete all remaining Primary and Secondary Endpoint assessments per protocol.

3. Referral to a service-specific substance abuse treatment program. Upon confirmation of non-prescribed illicit substance use, the study medical provider will initiate a referral to the participant's service-specific substance abuse treatment program in accordance with applicable military regulations, to include:
   - U.S. Army: Army Substance Abuse Program (ASAP) per AR 600-85
   - U.S. Navy/U.S. Marine Corps: Substance Abuse Rehabilitation Program (SARP) per OPNAVINST 5350.4E
   - U.S. Air Force/U.S. Space Force: Alcohol and Drug Abuse Prevention and Treatment (ADAPT) Program per AFI 44-121

The referral will be documented in the participant's source records and communicated to the participant's primary mental health provider. The study team will coordinate with the participant's unit to facilitate the referral while adhering to applicable privacy protections under HIPAA and 42 CFR Part 2.

4. Study Exit Plan. The participant will be provided with a Study Exit Plan (see Section 8.6.2) and will be encouraged to continue treatment with their primary mental health team.
5. Notification and reporting. The Principal Investigator will be notified, and the event will be documented in the deviation log if applicable. The Independent Safety Monitor will be consulted. Reporting to the IRB, DSMB, and sponsor will occur in accordance with each entity's reporting requirements.

Adjudication of Positive Urine Drug Screens

Before a positive urine drug screen is classified as confirmed illicit substance use, the study medical provider will complete the following adjudication steps:

- Review all current concomitant medications, including over-the-counter products and herbal supplements, for potential cross-reactivity with the screening immunoassay.
- Assess dietary and environmental exposures that may account for the positive result (e.g., poppy seed consumption, passive cannabis exposure).
- Obtain confirmatory testing via gas chromatography–mass spectrometry (GC-MS) or liquid chromatography–tandem mass spectrometry (LC-MS/MS) when the initial immunoassay result is equivocal or when a plausible alternative explanation exists.
- Consult the Independent Safety Monitor for adjudication in ambiguous cases.

A positive drug screen will not result in study termination if the result can be attributed to a pre-approved concomitant medication, a documented dietary practice, or is otherwise determined to be a false positive following confirmatory testing and Independent Safety Monitor review. Positive results for MDMA within 5 days following a Dosing Session are expected and will not be considered non-prescribed use, consistent with the Medical Review Officer notification procedures described in the Legal and Ethical Considerations section of this protocol.

9.6 Cardiac Safety

9.6.1 Additional Cardiac Screening

Anyone with a history of a cardiac or cardiovascular condition will be referred to cardiology for further evaluation, potential intervention, and potential clearance to enroll in the study per inclusion/exclusion criteria and local standard of care determined by the evaluating cardiologist.

9.6.2 ΔQTc Max

ΔQTc max in milliseconds (ms) is the QTc reading at 2 hours compared to the baseline QTc. A Holter 6-lead EKG monitor will capture EKG readings during each of the 3 dosing sessions for every participant. Measurements of QTc will be performed at baseline, 2 hours, and prior to discharge. The QTc represents the heart rate-corrected measure of cardiac depolarization and repolarization. An increase in QTc of greater than 60 ms compared to baseline or an absolute QTc > 500 ms are considered evidence of unsafe prolongation. Exceeding these thresholds would indicate a ~1% risk for torsades de pointes ventricular tachycardia, the most common lethal drug-induced arrhythmia. Previous studies do not suggest an increase in ventricular arrhythmias when MDMA is given as a single agent, but the impact of MDMA on the QTc is not well-studied. The most important time to assess the QTc is at CMax, the time of peak serum drug concentration. This is estimated to occur at 2 hours post oral dosing. Participants must be at rest prior to acquiring the baseline, 2-hour, and predischarge recordings in order to decrease motion artifact that can interfere with accurate EKG interpretation.

Following each dosing session, the EKG data will be downloaded to the H-Scribe reading station. The Veritas software will automatically scan the recording for evidence of cardiac arrhythmias. The cardiologist will review the data and measure the QTc at the appropriate timepoints. Importantly, the cardiologist will confirm the absence of significant cardiac arrhythmias. Finally, if the participant logged any episodes of symptoms, the EKG will be assessed at that timepoint (identified by the recording of an event using the appropriate button on the Holter and the event log recorded by the research team) to seek symptom-rhythm correlation.

9.6.3 Holter Monitoring During Dosing Sessions

Prior to investigational drug administration during each Dosing Session, Baxter H3+ 5-lead Holter monitors will be applied to all participants. These lightweight devices offer continuous 3-channel EKG recording for up to 48 hours using a single AAA battery and store data internally. Before each session, the Holter monitor will undergo a maintenance inspection, a fresh battery will be inserted, and electrodes will be placed in a standard 5-lead configuration (RA, LA, RL, LL, and V) following appropriate skin preparation to ensure signal quality. The device will be secured to the participant using either an adhesive pouch or carry case clipped to clothing. The LCD display will be used to confirm signal quality prior to drug administration.

Holter recordings will be collected at three prespecified timepoints: immediately prior to dosing (0 hours), 2 hours after the initial dose (presumed CMax), and at the end of the Dosing Session (6-8 hours after the initial dose). For each Holter recording, the participant will be asked to lie recumbent and motionless for 5 minutes. At the start of each 5-minute resting period, an investigator will press the “event marker” button on the Holter device.

If a participant reports any symptoms such as chest discomfort, palpitations, dizziness, light-headedness, pre-syncope, syncope, or shortness of breath, the investigator will also press the event marker button and document the time and symptom in the Dosing Session log. Corresponding vital signs, including blood pressure, will be measured and recorded in the vital signs log.

At the conclusion of the Dosing Session, all recordings will be transferred via USB to the H-Scribe Holter Analysis System, which utilizes the VERITAS algorithm for signal processing. Offline review and analysis—conducted on a non-networked computer—will include assessment of QT interval, QRS morphology and duration, ST segment changes, heart rate variability, and rhythm disturbances. Following device removal, the monitor will be cleaned in accordance with the manufacturer's instructions.

9.6.4 Cardiac Data Collection Procedures

- The Holter monitors must be time-synched with the study clock
- Prior to dosing, the participant should rest supine for 5 minutes. Then, the event button should be pressed on the Holter, and the time should be noted in the log. And the participant should lie still for another 60 seconds to acquire baseline EKG. After 60 seconds, the participant may be administered the study drug.
- At 2 hours and at the end of the dosing session (8 hours post-dosing), the participant should rest supine for 5 minutes. Then, the event button should be pressed on the Holter, and the time should be noted in the log. And the participant should lie still for another 60 seconds to acquire EKG reading. The participant may move again after 60 seconds.
- Holter monitor readings should also be repeated at any time the patient reports cardiac symptoms: chest pain, shortness of breath, palpitations, lightheadedness, or syncope

The study cardiologist will be responsible for reading, interpreting, and reporting the results of each of the Holter monitor readings to the study team and Independent Safety Monitor within 7 days after each Dosing Session.

9.6.5 EKG and QTc Stopping Criteria

EKG readings will be collected via Holter monitors at the 0-hour pre-dosing, 2-hour post-dosing, and end-of-session timepoints during Dosing Sessions. QT measurements will be made in the resting, supine state. EKG stopping criteria:

- Uncorrected QT > 600 ms OR QTc > 500 ms using the Fridericia correction for heart rate (QT/RR^⅓; QT in ms and RR in seconds)
- Increase from baseline QTc > 60 ms
- Atrioventricular block second degree Mobitz 2 or third degree
- Ventricular tachycardia, either polymorphic or monomorphic
- Atrial fibrillation
- Atrial flutter
- Any symptomatic arrhythmia including bradycardia (heart rate < 50 beats per minute (bpm) with cardiac symptoms, or < 40 lasting > 5 minutes without cardiac symptoms)
- Resting tachycardia (heart rate > 100 bpm with cardiac symptoms or > 130 bpm lasting > 5 minutes without cardiac symptoms)

If one of the EKG stopping criterion are met during a Dosing Session with an initial MDMA dose of:

- 40 mg or 80 mg – The case will be discussed in detail with the study cardiologist and Independent Safety Monitor to be considered for withdrawal from the study as a post-randomization early termination if additional Dosing Sessions still remain.
- 120 mg – The case will be discussed in detail with the study cardiologist and Independent Safety Monitor to be considered for reduction of the initial dose to 80 mg for the next Dosing Session if there had been no clinically relevant EKG findings or cardiac symptoms in a previous 80 mg Dosing Session. The participant will also be considered for withdrawal from the study as a post-randomization early termination if additional Dosing Sessions still remain.

9.6.6 Restarting Study Intervention After Meeting EKG Stopping Criteria

If a QTc > 500 ms OR Uncorrected QT > 600 ms using the Fridericia correction for heart rate (QT/RR^⅓; QT in ms and RR in seconds) or an increase from baseline of QTc > 60 ms is detected, a complete review of concurrent medications that might contribute to delayed repolarization or inhibit CYP2D6 will be made. If those drugs can be terminated and QTc returns to baseline after five half-lives, then the participant will remain eligible for subsequent Dosing Sessions.

No rechallenge will be attempted if any symptomatic arrhythmia or if asymptomatic ventricular tachycardia, atrial fibrillation/flutter, or AV block >Mobitz 1 is noted.

9.7 Vital Signs

MDMA is an indirect sympathomimetic drug, leading to increased release of norepinephrine, the most important neurotransmitter for modulating heart rate and peripheral vascular resistance. MDMA is anticipated to cause an increase in heart rate, blood pressure, and temperature. When used alone, MDMA at 1.5 mg/kg increased mean heart rate (by 28 beats/min), systolic blood pressure (by 25 mmHg), and diastolic blood pressure (by 7 mmHg).[249] In another study using comparable dosages of MDMA (75 mg and 125 mg), 33% of participants experienced systolic blood pressure > 160 mm Hg, 29% had a heart rate >100 bpm, and 19% had a temperature > 38°C, with no cardiac adverse events noted.[47] A greater proportion of participants dosed with 125 mg had each of these findings compared to those dosed with 75 mg. These blood pressure, heart rate, and temperature increases would be more concerning if they represented chronic values. Although they present less danger when maintained for several hours in participants without overt cardiovascular disease, our protocol clearly details appropriate stopping criteria relevant to each of these vital signs to ensure participant safety.

Vital signs will be collected at least once during screening and for at least four timepoints during each Dosing Session (at pre-dosing baseline, 2 hours (± 15 minutes) post initial MDMA dose at the presumed maximum serum concentration of MDMA, 4 hours (± 15 minutes) post initial MDMA dose, and at the conclusion of the Dosing Session (see Table 13) only after lying supine at rest for at least 5 minutes.

9.7.1 Blood Pressure Stopping Criteria

While not under the acute effects of the study drug, uncontrolled hypertension defined as resting state blood pressures of > 140 mmHg systolic or > 90 mmHg diastolic (i.e., "140/90") assessed on three separate occasions is an exclusion criteria for study enrollment (see Section 5.2 Exclusion Criteria). Participants may have well-controlled hypertension that has been successfully treated with anti-hypertensive medicines, if additional screening is passed to rule out underlying cardiovascular disease.

During Dosing Sessions, systolic blood pressures outside of 90-160 mmHg or diastolic blood pressures outside of 60-100 mmHg will be rechecked after at least 5 minutes of rest. Blood pressures that remain outside of the aforementioned ranges for > 5 minutes will be considered an adverse event and if found at the pre-dosing baseline, will preclude administration of the initial dose of MDMA. Participants with systolic blood pressures of 90-160 mmHg or diastolic blood pressures of 60-100 mmHg at the pre-dosing baseline during the Dosing Session will still be allowed to be dosed with MDMA as long as their blood pressures are typically ≤ 140/90 mmHg and they do not meet criteria for uncontrolled hypertension; this accounts for the fact that individuals without essential hypertension may still present with transient stress-related hypertension in a medical setting (colloquially known as "white coat hypertension") which can be anticipated due to the anxiety leading up to a Dosing Session and is clinically insignificant if asymptomatic and the blood pressure is ≤ 160/100 mmHg.

Blood pressures > 180/120 mmHg *with* (hypertensive emergency) or *without* (hypertensive urgency) associated hypertensive symptoms (headache, blurred vision, focal neurologic findings, chest pain/pressure/discomfort, acutely severe back pain, dyspnea, nausea, or vomiting) will be considered an adverse event of special interest (AESI; see Section 9.13.5), will preclude administration of a supplemental dose during the Dosing Session, and will require further outpatient evaluation prior to being considered for continuation in the study.

Hypertensive emergency (blood pressure > 180/120 mmHg associated with headache, blurred vision, focal neurologic findings, chest pain/pressure/discomfort, acutely severe back pain, dyspnea, nausea, or vomiting) will require the available study medical provider evaluate the participant and determine whether the best course of action is to either transport the participant to the WRNMMC Emergency Department or to initiate a Code Blue (Supplement 1). Once safe to do so and if all Dosing Sessions have not already been completed, an episode of hypertensive emergency will also necessitate the participant be withdrawn from the study as a post-randomization early termination (see Section 7.3.2.1).

9.7.2 Restarting Study Intervention After Meeting Blood Pressure Stopping Criteria

Participants with uncontrolled hypertension (> 140/90 mmHg on three recent separate occasions) not in the setting of acute MDMA administration or hypertensive urgency (asymptomatic blood pressures >180/120 mmHg) at any point during the study may be considered for continued study participation per protocol only after further evaluation and clearance by their primary care manager or cardiologist, which must include review of antihypertensive therapy and participant adherence to appropriate antihypertensive intervention. After further evaluation and clearance, the study team, in consultation with ISM, will then reevaluate if the participant meets inclusion/exclusion criteria for continued participation in the study per protocol.

If a participant is undergoing outpatient evaluation for hypertension while enrolled in the study, their next Dosing Session may be delayed by up to one additional week without deviating from the protocol (e.g., their next Dosing Session may be 3-6 weeks after their last Dosing Session instead of 3-5 weeks). If all inclusion/exclusion criteria are met in time for the participant to proceed with their next Dosing Session within 3-6 weeks of their previous Dosing Session, the participant will then be eligible to continue with participation in the study. If all inclusion/exclusion criteria are not met and all Dosing Sessions have not already been completed, the participant will be withdrawn from the study as a post-randomization early termination (see Section 7.3.2.1).

9.7.3 Heart Rate Stopping Criteria

A heart rate < 50 or > 100 bpm will be rechecked after 5 minutes of rest. Bradycardia and tachycardia, defined as a heart rate of < 50 or > 100 bpm, respectively, lasting for > 5 minutes will be considered adverse events. A participant will not be offered the next dose of MDMA during a Dosing Session – whether it be an initial or supplemental dose – if they meet any of the following criteria:

Resting bradycardia (heart rate lasting > 5 minutes at < 50 bpm with cardiac symptoms or < 40 bpm without cardiac symptoms)

Resting tachycardia (heart rate lasting > 5 minutes at > 100 bpm with cardiac symptoms or > 130 bpm without cardiac symptoms)

9.7.4 Restarting Study Intervention After Meeting Heart Rate Stopping Criteria

Participants that meet any of the heart rate stopping criteria at any point during the study may be considered for continued study participation per protocol only after further evaluation and clearance by their primary care manager or cardiologist, which must include review of all medications and participant adherence to appropriate recommended interventions. After further evaluation and clearance, the study team, in consultation with ISM, will then reevaluate if the participant meets inclusion/exclusion criteria for continued participation in the study per protocol.

If a participant is undergoing outpatient evaluation for clinically concerning bradycardia or tachycardia while enrolled in the study, their next Dosing Session may be delayed by up to one additional week without deviating from the protocol (e.g., their next Dosing Session may be 3-6 weeks after their last Dosing Session instead of 3-5 weeks). If all inclusion/exclusion criteria are met in time for the participant to proceed with their next Dosing Session within 3-6 weeks of their previous Dosing Session, the participant will then be eligible to continue with participation in the study. If all inclusion/exclusion criteria are not met and all Dosing Sessions have not already been completed, the participant will be withdrawn from the study as a post-randomization early termination (see Section 7.3.2.1).

9.7.5 Temperature Stopping Criteria

During Dosing Sessions, a temperature >38°C (> 100.4°F) will be rechecked after at least 5 minutes of rest. Temperature > 38°C (> 100.4°F) for > 5 minutes will be considered an adverse event and, if detected prior to the initial MDMA dose, will preclude administration of the initial dose of MDMA that day. Temperatures > 39°C (> 102.2°F) detected prior to the supplemental

dose will preclude the administration of the supplemental dose. Temperatures > 40°C (> 104.0°F) are considered life-threatening and require immediate notification of the study physician and Independent Safety Monitor for determination of a treatment plan for reducing the fever; if other modifiable potential causes for the life-threatening fever are not identified, the fever will be determined to be related to the study drug, and the participant will be disenrolled. All participants with temperatures < 40°C will be permitted to complete the next dosing session as scheduled.

9.7.6 Restarting Study Intervention After Meeting Temperature Stopping Criteria

Any temperature ≥ 38°C (≥ 100.4°F) and < 40°C (< 104.0°F) will be reviewed by the study team and if determined to be a mild adverse event the participant will be allowed to continue with the next dosing session as scheduled. For temperatures ≥ 40°C (≥ 104.0°F) the study team, in consultation with ISM, will reevaluate if the participant meets inclusion/exclusion criteria for continued participation in the study per protocol.

9.8 Hepatic Safety

9.8.1 Drug-Induced Liver Injury Stopping Criteria

A liver panel will be obtained for all participants during screening, prior to each Dosing Session (P_3, $I_{1.3}$, and $I_{2.3}$), and the day after each Dosing Session ($I_{1.1}$, $I_{2.1}$, and $I_{3.1}$). The liver panel will include measures of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total/direct/indirect bilirubin, among other clinically relevant measures of liver function (see Section 9.11 Clinical Safety Laboratory Tests).

In accordance with FDA Guidance on Drug-Induced Liver Injury,[250] a participant will be withdrawn from the study and considered a post-randomization early termination (see Section 7.3.2.1) if they meet any of the following criteria:

1. AST or ALT **>8x** upper limit of normal (ULN)
2. AST or ALT **>5x** ULN for **>14 days**
3. AST or ALT **>3x** ULN *and* [**total bilirubin >2x** ULN *or* international normalized ratio **(INR) >1.5**]
4. AST or ALT **>3x** ULN **with new-onset symptoms of hepatic injury** (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%)

INR and complete blood count (CBC) with differential will be obtained reflexively if AST or ALT >3x ULN or as clinically indicated.

When a participant meets liver injury stopping criteria, the study team will refer the participant to their primary care manager and/or hepatology for follow-up unless clinical severity requires urgent management, in which case participants will be directed to their nearest emergency department for further evaluation. All instances of elevated liver enzymes will be reported in an expedited manner to the Independent Safety Monitor, Sponsor, and drug manufacturer.

9.8.2 Close Observation for Liver Injury

When AST or ALT **>3x** ULN without meeting any of the four liver injury stopping criteria (see Section 9.8.1), Close Observation procedures will be initiated for the participant in accordance with FDA Guidance on Drug-Induced Liver Injury.[250]

Close Observation procedures include:

- Repeat liver panel (including AST, ALT, and total bilirubin) every two to three days.
    - Frequency of retesting can decrease to once per week or less if abnormalities stabilize and the participant has no symptoms of hepatic injury (new-onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%).
    - Retesting may discontinue after two consecutive liver panels approximately one week apart that both indicate any previously elevated lab values have normalized to their pre-dosing baseline.
- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a more detailed history of concomitant drug use (including prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, prothrombin time).
- Consider gastroenterology or hepatology consultations.
- Delay next Dosing Session by up to one additional week (i.e., next Dosing Session may be 3-6 weeks instead of 3-5 weeks after previous Dosing Session) until either:
    - The study team decides withdrawal from the study is necessary as a post-randomization early termination to ensure the participant's safety.
    - Close Observation procedures are not completed in time to ensure the next Dosing Session can take place within 6 weeks after the previous Dosing Session, in which case, the participant will be withdrawn from the study as a post-randomization early termination.
    - Close Observation procedures have been completed and the Independent Safety Monitor determines the participant is normalized to their pre-dosing baseline, in which case, study participation may continue per protocol if all other restart criteria are met (see Section 9.8.3).

When initial post-dosing AST or ALT are **2-3x** ULN, a follow-up liver panel will be obtained within two to three days. If the previously elevated AST or ALT is:

- Uptrending, initiate Close Observation procedures.
- Downtrending, continue study participation without additional monitoring or Close Observation procedures.

9.8.3 Restarting Study Intervention After Close Observation for Liver Injury Criteria Are Met

For a participant who undergoes Close Observation procedures to monitor for potential liver injury (see Section 9.8.2), they may continue with study participation per protocol if all of the following criteria are met:

- Two consecutive liver panels approximately one week apart both indicate that any previously elevated lab values have normalized to their pre-dosing baseline.

- All additional hepatic workup per Close Observation procedures has been completed.
- Independent Safety Monitor has reviewed all relevant history, labs, and workup per Close Observation procedures and determines that any concerning etiologies for potential liver injury have been sufficiently ruled out.
- All of the above has occurred within enough time to ensure that the next Dosing Session can take place within 6 weeks after the previous Dosing Session.

If all of the above restart criteria cannot be met, the participant will be withdrawn from the study as a post-randomization early termination (see Section 7.3.2.1).

9.9 Sodium Monitoring

9.9.1 Hyponatremia Stopping Criteria

The study intervention will be withheld if:

- Serum sodium is found to be < 130 mmol/L prior to dosing, or
- If the participant develops symptomatic hyponatremia (e.g., confusion, seizures, altered mental status) at any point during the study.

9.9.2 Restarting Studying Intervention after Hyponatremic Event

The study intervention may be restarted if:

- Serum sodium has normalized to ≥ 135 mmol/L, **and**
- The participant is free of symptomatic hyponatremia (e.g., confusion, seizures, altered mental status), **and**
- The restart has been reviewed and approved by the PI and Independent Safety Monitor.

9.10 Physical Examinations

A physical exam will be conducted by a qualified non-study clinician within 28 days prior to enrollment, and this physical exam will be reviewed by a study physician for the purpose of determining enrollment. A second confirmatory physical exam will be conducted by a qualified study physician between enrollment and the third preparatory session for the purpose of clearing the participant for dosing. The confirmatory physical exam will include the following:

- Examination of head, heart, lungs, abdomen, and extremities.
- Neurological exam.
- Blood pressure, pulse, and body temperature measurement.
- Height and weight, which will be used to calculate BMI.

9.11 Clinical Safety Laboratory Tests

Clinical safety laboratory tests will be collected at timepoints that are specified in Table 11 and Table 12. Screening labs will be collected at the participants' nearest Military Health System clinical lab. The results of the screening labs will be reviewed by an investigator with the appropriate medical credentials to determine eligibility. Eligibility will be determined based on whether the participant meets all inclusion/exclusion criteria relevant to lab findings: negative urine pregnancy test, negative urine drug screen, liver panel9.8, thyroid function testing that

indicates normal thyroid function, basic metabolic panel and complete blood count that do not indicate any clinically relevant findings per medical investigator clinical judgment.

Clinically significant lab findings before the first dose of the IP will be documented as clinical history or a pre-existing condition. These findings will be reported as AE or SAE only if the pre-existing condition worsens following administration of the IP. Clinically significant abnormal lab findings or other abnormal assessments that are detected after administration of the IP during the study will be reported as AEs or SAEs, unless the lab findings fall within the established local laboratory reference ranges. Chronic clinically significant labs or clinical abnormalities will be followed until they return to normal or baseline, stabilized after baseline with the probability of becoming chronic, or a satisfactory explanation is provided by the investigator.

Table 14. Clinical Safety Laboratory Tests

Lab	Indices	Screening		Throughout Enrollment		Total
		Number of collections	Amount per collection (ml)	Number of collections	Amount per collection (ml)	Cumulative amount collected (ml)

CBC	• Hematocrit
	• Hemoglobin
	• Red Blood Cell (RBC) indices:
	  ○ RBC count
	  ○ Percentage and absolute differential counts
	  ○ Red cell distribution width (RDW)
	  ○ Mean corpuscular volume (MCV)
	  ○ Mean corpuscular hemoglobin (MCH)
	  ○ Mean corpuscular hemoglobin concentration (MCHC)
	• White blood cell (WBC) indices:
	  ○ RBC count
	  ○ Percentage
	  ○ Neutrophils
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils
		1	4	-	-	4

Lab	Indices	Screening		Throughout Enrollment		Total
Basic Metabolic Panel (BMP)	• Calcium, serum • Carbon dioxide • Chloride, serum • Creatinine • Glucose • Potassium, serum • Sodium, serum • Blood urea nitrogen (BUN): creatinine ratio	1	?	-	-	?
Liver Panel	• Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) • Albumin, serum • Alkaline phosphatase • Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase • Bilirubin, total and direct • Protein, total	1	?	6	?	?
PT/INR	• Prothrombin Time (PT) • International Normalized Ratio (INR)	-	-	6	2.7	16.2
TSH	• Thyroid Stimulating Hormone (TSH)	1	5	-	-	5
T3	• Triiodothyronine	1	5	-	-	5
T4	• Thyroxine	1	5	-	-	5

Lab	Indices	Screening		Throughout Enrollment		Total
bHCG Screen, Urine	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for females of childbearing potential)	1	1	1	1	2
Drug Screen, Urine	• Amphetamines • Barbiturates • Cocaine • Methadone • Opiates • Oxycodone • Fentanyl • Phencyclidine plus (PCP) • Cannabinoids • Benzodiazepines	1	1	-	-	2
Point-of-care (POC) bHCG Screen, Urine	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for females of childbearing potential)	-	-	3	0.15	0.45
POC Drug Screen, Urine	• Amphetamines • Barbiturates • Cocaine • Methadone • Opiates • Oxycodone • Fentanyl • Phencyclidine plus (PCP) • Cannabinoids • Benzodiazepines	-	-	3	30	90

9.11.1 Pregnancy Testing

All participants who are able to become pregnant will receive urine pregnancy testing five times throughout the study: once at the lab as part of screening procedures, point-of-care testing the morning before each of the three dosing sessions, and their final test at a lab at least 3 days after their final dosing session.

Fisher Healthcare™ brand Sure-Vue™ Urine hCG Test Kits will be used to conduct point-of-care pregnancy screenings the morning of each Dosing Session. Participants will provide urine samples in sterile Thermo Scientific™ Samco™ Clicktainer™ Vials and Specimen Containers. The study team member will then place the specimen on a level surface and allow the specimen to equilibrate to room temperature. The study team member will then use the provided dropper to transfer 3 drops of urine onto the specimen well of the test device. The test will be read after 3-4 minutes. A positive test is indicated by two red lines, one in the control region and one in the test region.

If the participant has a positive result, they will discontinue all subsequent Dosing Sessions but remain in the study for the Integration Sessions associated with the most recent Dosing Session.

9.12 Other Assessments

9.12.1 Pharmacogenomics

Pharmacogenomics (PGx) refers to DNA analysis utilizing mucosal cells collected from a buccal saliva swab. PGx can detect genetic polymorphisms that affect metabolism of pharmacotherapeutics including MDMA. This study will use the Genomind Professional PGx Express test which includes the genotyping of 73 targets. Sixty-two single nucleotide polymorphisms (SNPs) are analyzed by quantitative polymerase chain reaction (qPCR), 8 by multiplex qPCR, 2 [SERT gene] by qPCR, as well as CYP2D6 copy number variation also by qPCR. Human Leukocyte Antigen (HLA) type HLA-B *15:02 is tested by qPCR using a surrogate SNP. HLA-A 31:01 is tested using a custom real-time qPCR. This assessment will explore if these genetic polymorphisms affect MDMA safety, efficacy, and tolerability.

9.12.2 Neurable EEG Headphones

Neurable's over-the-ear headphones, known as the "MW75 Neuro LT", utilizes dry-electrode sensors embedded within each ear cup to measure electroencephalography (EEG) signals from the scalp. The system consists of 12 dry EEG electrodes with a ground and reference electrode both located on each side of the earcup. Each electrode is constructed using conductive Ag/AgCl fabric weaved directly into the removable earcup pieces. The system is capable of streaming raw EEG data to a PC via Bluetooth transmission at a 250 Hz sampling rate and with 24-bit resolution. Data is streamed through the Neurable Research Kit software which subsequently generates a LabStreamingLayer (LSL) stream that can be used for time synchronization with external stimuli or other physiological data streams being collected simultaneously. In addition to its EEG capability, the MW75 Neuro LT also has premium audio functionality, including adaptive noise cancellation, pass through audio, and beamforming microphones suitable for use during MDMA dosing sessions. The Neurable's EEG assessment will explore the immediate

effects of MDMA on cognitive biomarkers (such as power band changes, hemispherical asymmetry, coherence fluctuations, etc.) during dosing sessions as well as their longitudinal changes as participants undergo multiple treatment sessions over time.

The headset is not an FDA approved medical device. The data collected will be for exploratory purposes only and won't be used to impact treatment decisions or diagnosis. EEG and primary outcome efficacy data will be shared with Neurable.

9.13 Adverse Events, Serious Adverse Events, Adverse Events of Special Interest and Other Safety Reporting

The PI and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an Adverse Event (AE), Serious Adverse Event (SAE), Adverse Event of Special Interest (AESI), or Treatment Emergent Adverse Event (TEAE) and remain responsible for following up on all AEs.

AEs will be reported by the participant (or, when appropriate, by a caregiver or surrogate). The collection period of AEs is from the time of the signed study ICF until completion of the Study Completion visit. All AEs should be recorded regardless of the causality of the event. The PI will elicit information through non-leading open-ended questioning and examination of the participant about the occurrence of the AE. For each event, the following information will be recorded in the participant's record and transcribed into the AE section of the CRF and SAE form.

- Description of signs and/or symptoms. Whenever possible, the specific diagnosis for the event will be recorded. If a diagnosis cannot be made, each sign or symptom will be recorded separately (e.g., nausea and vomiting would be recorded as two separate events)
- Classification of the event as an SAE
- Classification of the event as an AESI
- Classification of the severity of the event (See Table 15)
- Classification of the event's expectedness
- Causality in relation to study medication (See Table 16)
- Action taken with study medication
- Adverse event outcome
- Event onset date
- Event stop date

If an AE requires medical care by a provider outside of the study, a study team member will follow-up with the participant within one week to ensure that the appropriate appointment(s) are established as needed.

9.13.1 Adverse Event (AE) Definition

An AE is any untoward medical occurrence in a clinical study participant which may or may not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of IP, whether or not related to the IP.

Note: For the purpose of this study, an AE will be considered any event that occurs within the study from study Informed Consent to Study Completion. Per FDA guidance for psychedelic research,[239] particular attention should be paid to abuse-related AEs, which may include, but are not limited to:

- Euphoria, stimulation, hallucinations (see guidance for industry on how to conduct abuse potential evaluation in Assessment of Abuse Potential of Drugs (2017)).[239]

The PI or qualified designee should carefully record any AE that occurs within the study time frame. Whenever possible, a diagnosis rather than a list of signs and symptoms is preferred. Treatment or intervention of an AE should not be reported as an event unless it causes another event. The event necessitating the treatment or intervention should be reported. AEs should be followed until the events have subsided, returned to baseline or in case of permanent impairment, until the condition stabilizes.

9.13.2 AE Severity Grading Criteria

All AEs will be assessed for severity by the investigator. Inherent in this assessment is the medical and clinical consideration of all information surrounding the event including any medical intervention required. AEs will be graded according to the scale in Table 15. Events and laboratory values that fall within established local laboratory reference ranges will not be considered AEs, regardless of if the event or value meets criteria for grading per Table 15. The CRF for AEs will reflect only the highest severity for continuous days an event occurred.

Table 15. General Adverse Event Grading Scale

Grade	Description	Definition
1	Mild	Does not interfere with routine activities; minimal level of discomfort
2	Moderate	Interferes with routine activities; moderate level of discomfort
3	Severe	Unable to perform routine activities; significant level of discomfort
4	Life-threatening	Hospitalization, ER visit, or urgent intervention indicated for life-threatening event
5	Fatal	Death

Note: The terms “serious” and “severe” are *not* synonymous. The general term “severe” is often used to describe the intensity (severity) of a specific event. The event itself may be of relatively minor medical significance (e.g., severe headache). A severe headache does not necessarily need to be considered serious unless it meets the criteria of a serious adverse event (Section 9.13.4).

Any related and/or unexpected Grade 4 or 5 event must be reported as an SAE, and must be reported to the FDA within 7 calendar days per 21 CFR § 312.32(c)(2).[251]

Appendix B details the grading scale for vital signs.

Appendix C details the grading scale for common AEs.

Appendix D details the grading scale for lab values.

9.13.3 AE Causality Assessment

The PI will assess the causal relationship between the AE and the study IP or the study procedure. Causality will be reported separately for each study intervention received by the participant. A physician must assign a relationship of each AE to the receipt of the investigational product using the relationship categories in Table 16.

Table 16. Causality Relationships

Relationship	Description
Not related	No relationship to investigational product. Applies to those events for which evidence exists that there is an alternate etiology.
Unlikely	Likely unrelated to the investigational product. Likely to be related to factors other than the investigational product but cannot be ruled out with certainty.
Possible	An association between the event and the administration of investigational product cannot be ruled out. There is a reasonable temporal association, but there may also be an alternative etiology, such as the participant's clinical status or underlying factors (including other therapy).
Probable	There is a high degree of certainty that a relationship to the investigational product exists. There is a reasonable temporal association, and the event cannot be explained by known characteristics of the participant's clinical state or factors including other therapy.
Definite	An association exists between the receipt of investigational product and the event. An association to other factors has been ruled out.

9.13.4 Serious Adverse Events (SAE)

All SAEs that occur from the time of signed study ICF through the final Study Completion visit should be reported. Any SAE that is continuing at the time of the Study Completion visit will be followed until the outcome of the event is known. Whenever possible the PI should report the overall diagnosis of the event(s) rather than the signs and symptoms associated with the event(s). Treatment or intervention of an event should not be reported as an SAE. The event necessitating treatment or intervention should be reported.

An AE or suspected adverse reaction is considered serious if it results in any of the following outcomes:

- Death
- Life-threatening AE
    - In the view of either the investigator or sponsor, its occurrence places the participant at immediate risk of death
    - It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization

  - Hospitalization does not include the following: emergency room visit (< 24 hours) or same day surgeries (as outpatient/same day/ambulatory procedures, if the surgery was preplanned prior to entering the study).
  - If during a preplanned hospitalization, an event occurs that was not part of the preplanned hospital admission (e.g., thromboembolic event), then the event prolonging the hospitalization and not associated with the preplanned event should be reported.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment:
  - They may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above in this definition.
  - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

SAEs will be reported to DHA R&D - MRDC ORA PSSO, IRB, Independent Safety Monitor, and drug manufacturer on the SAE/AESI report form within 24 hours of discovery. Per 21 CFR § 312.32(c)(2),[251] Related/unexpected SAEs will be reported to the FDA within 7 days of discovery; unrelated SAEs are reported with the annual report.

9.13.5 Adverse Events of Special Interest (AESI)

AESIs are significant AEs that are judged to be of special interest because of clinical importance, known or suspected class effects, or based on nonclinical signals. The event may require further investigation and, depending on the nature of the event, submission to the FDA or other applicable regulatory authorities. For the purpose of this trial, AESIs have been predefined.

AESIs will be assessed at the time points specified in Table 17 and reported to DHA R&D - MRDC ORA PSSO, IRB, Independent Safety Monitor, and drug manufacturer on the SAE/AESI report form within 24 hours of discovery.

Any AESI that also meets the criteria of an SAE will be recorded as an AESI and SAE on the SAE/AESI report form prior to submission to each entity. Per 21 CFR § 312.32(c)(2),[251] SAEs that are related and/or unexpected will be reported to the FDA within 7 days of discovery.

AESIs will include the following:

- Cardiac arrhythmias, or AEs that are indicative of QT interval prolongation, including (but not limited to) Torsade de pointes, sudden death, ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation and flutter, palpitations, non-postural syncope and seizures
- Cardiac disorders (e.g., acute MI, angina pectoris, ischemic chest pain)
- Drug diversion, drug abuse, and drug accountability (e.g., accidental poisoning, behavioral addiction, dependence, drug abuser, drug diversion, overdose, intentional

overdose, intentional product misuse, poisoning deliberate, prescribed overdose, substance abuser, hallucination dissociative state, psychosis, aggression, drug tolerance, habituation, drug withdrawal syndrome, euphoria-like effect, substance related disorders)
- Central nervous system vascular disorders (e.g., ischemic central nervous system vascular conditions)
- Seizures
- Hypertensive crisis (blood pressure > 180/120)
- Malignant hypertension (blood pressure >180/120 with signs or symptoms of end-organ damage)
- Drug-induced liver injury (see Section 9.8.1 for criteria)
- Suicide, suicide attempt, self-injury in the context of suicidal ideation, C-SSRS Suicidal Ideation score of 4 or 5, and/or suicidal ideation judged as serious or severe by the Sponsor.

AESIs will be followed until the event is resolved, returned to baseline, or determined to be chronic.

9.13.6 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered unexpected if:

- It is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed
- It is mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but is not specifically mentioned as occurring with the particular drug under investigation

For example:

- Hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis
- Cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents

9.13.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an adverse reaction that meets three criteria: suspected, unexpected, and serious.

- Suspected: There is a reasonable possibility that the drug caused the adverse drug reaction.
- Unexpected: An adverse reaction, the nature or severity of which is not consistent with the applicable product information.[92]
- Serious: Meets the definition of SAE as described in Section 9.13.4.

SUSARs must be reported to the FDA within 15 calendar days per 21 CFR § 312.32(c)(1)(i).[251]

9.13.8 Treatment Emergent Adverse Events (TEAEs)

Treatment Emergent Adverse Events (TEAEs) refer to any AEs that arise or worsen after the administration of the investigational product during a clinical trial. These events are closely

monitored to assess the safety profile of the treatment and determine its potential risks to participants. TEAEs are categorized based on severity (Table 15) and relationship to the investigational product (Table 16).

9.13.9 Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO)

UPIRTSOs, are unexpected AEs and SAEs, in the opinion of the PI, are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol and must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days.

UPIRTSOs meet all of the following criteria:

- Is unexpected (in terms of nature, severity, or frequency) given:
  - The procedures that are described in the protocol, IB, or informed consent document; and
  - The characteristics of the subject population.
- Is related or possibly related to participation in the study
- Suggests that the protocol places participants or others at a greater risk of harm than was previously known or recognized

These events encompass a broader category of events than SAEs and may include issues such as problems with loss of control of participant data or the investigational product; adverse psychological reactions; or breach of confidentiality.

The PI will determine whether a given incident, experience or outcome constitutes a UPIRTSO and will promptly (within 48 hours) report UPIRTSOs to the WRNMMC IRB and to the sponsor. The PI will then submit a written report within 10 working days to the WRNMMC IRB. Follow up reports should be submitted as soon as additional information becomes available. The summary of UPIRTSOs will also be included in the continuing review report submitted to the WRNMMC IRB. The study team will report UPIRTSOs to the United States Army Medical Research and Development Command (USAMRDC) Office of Human and Animal Research Oversight (OHARO) Office of Human Research Oversight (OHRO) as per USAMRDC Command Policy 17 “Event Reporting Requirements for Human Subjects Research Conducted by USAMRDC.”

9.13.10 Other Reportable Information

Other reportable AEs include but are not limited to the following:

- An AE occurring from an overdose (i.e., a dose higher than that indicated in the protocol) of study drug whether accidental or intentional
- An AE occurring from abuse (e.g., non-prescribed use of MDMA from non-study sources)
- An AE that has been associated with the discontinuation of the use of study IP
- A medication error such as an inadvertent or accidental exposure to study IP with or without an AE

Any event meeting the above-mentioned criteria must be reported to ORA, IRB, Independent Safety Monitor, drug manufacturer, and any other appropriate regulatory bodies within 24 hours

of discovery. These events should be followed until any AEs have subsided, returned to baseline, or in the case of permanent impairment, until the condition stabilizes.

9.13.11 Reporting of Adverse Events

AEs and SAEs will be assessed at all study visits, documented in the source records, and recorded on the sponsor-approved Adverse Event and Serious Adverse Event eCRFs using accepted medical terms and/or the diagnoses that accurately characterize the event.

Expected reportable events and events that are not related to study participation are reported on the Continuing Review (CR) Progress Report. CR is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

The PI will report SAEs to the sponsor's safety office (DHA R&D - MRDC ORA PSSO) according to the requirements in Table 17. A summary of the required information is provided in Table 18. When reporting via email, the subject lines should be formatted as follows:

> **Initial:** SAFETY REPORT – IND # xxx_____, Sponsor Study #S-xx-xx_____, Participant# _____, Event term: _____
>
> **Follow-Up:** SAE Case Number provided by PSSO (e.g., US-000123), SAFETY REPORT – IND # xxx_____, Sponsor Study #S-xx-xx_____, Participant#____, Event term: _____

In order to comply with regulations mandating sponsor notification of specified SAEs to the U.S. FDA within 7 calendar days, the PI must submit additional information as soon as it is available. The sponsor's representative will report unexpected SAEs associated with the use of the drug to the U.S. FDA as specified at 21 CFR Part 312.32 (c).[251]

Investigators must also follow all relevant regulatory requirements regarding the timely reporting of AEs to the WRNMMC IRB and the USAMRDC OHARO OHRO.

There may be instances when copies of medical records for certain cases are requested by the sponsor's safety office. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of the medical records before submission to the sponsor's safety office.

Table 17. Sponsor's Adverse Event Reporting Requirements

Event	Report	Notification Time	Notification Method
Serious Adverse Events	Serious Adverse Event/Adverse Event of Special Interest Report	Within 24 hours of event awareness[a]	Email: usarmy.detrick.medcom-usamrmc.mbx.sae-reporting@health.mil If email is not available, the information can be faxed or called in: Fax: 301-619-0197 Phone: 301-619-1005
	Independent Safety Monitor Report	Within 24 hours of event awareness	
Adverse Events of Special Interest	Serious Adverse Event /Adverse Event of Special Interest Report	Within 24 hours of event awareness[a]	
	Independent Safety Monitor Report	Within 24 hours of event awareness	
Pregnancy	Pregnancy Report	Within 24 hours of event awareness	
Adverse Event Related Withdrawals	Contact Office of Regulated Activities (ORA) Product Safety Surveillance Office (PSSO)	Within 5 business days of event awareness	
Safety-Related Deviations	Contact ORA PSSO	Within 5 business days of event awareness	

[a] Submission of the reports to the Office of Regulated Activities Product Safety Surveillance Office must not be delayed. Do not wait to receive the Independent Safety Monitor's report.

Table 18. Summary of Information Required When Reporting Adverse Events to Sponsor

Information to Include on the Serious Adverse Event/Adverse Event of Special Interest Report Form includes, but is not limited to:
Investigational New Drug application number, sponsor study number
Name of the investigational product
Investigator name and contact number
Participant identification number
Serious adverse event/Adverse Event of Special Interest term, description
Onset date
Date(s) of investigational product administration
Severity
Relationship to the investigational product
Participant's current status
Admission/Discharge Summary
Consultations
Medical record progress notes including pertinent laboratory/diagnostic test results

Any follow-up information should be provided on a new SAE/AESI report form with a sequential follow-up number starting with follow-up #1. The SAE/AESI report form should be used for any changes, revisions, or additional reports to the event.

The PI assumes responsibility for appropriate reporting of any UPIRTSO to the regulatory authorities and governing bodies according to the local regulations.

All SAEs and AESIs should be followed until resolved, returned to baseline, or determined to be chronic.

9.13.12 Pregnancy Reporting

Any participant who becomes pregnant while participating in the study will not undergo any additional Dosing Sessions, though will be offered the option to finish the Integration Sessions associated with their last Dosing Session and will also be invited to complete Primary and Secondary Endpoint measures as well as Study Completion procedures. The participant will be emergency unblinded as described in Section 6.4, after the final CAPS-5-R assessment.

Each pregnancy must be reported within 24 hours of identification by completing the Pregnancy Report Form and submitting it to the sponsor's safety office (DHA R&D - MRDC ORA PSSO) by email (usarmy.detrick.medcom-usamrmc.mbx.sae-reporting@health.mil).

The Investigator will monitor the pregnancy, including the status of the participant and her offspring by submitting Follow-up Pregnancy Report Forms to the sponsor's safety office (DHA R&D - MRDC ORA PSSO) by email: usarmy.detrick.medcom-usamrmc.mbx.sae-reporting@health.mil).

After the end of the pregnancy, the following information must be recorded on the Pregnancy Report and submitted to the sponsor's safety office by email (usarmy.detrick.medcom-usamrmc.mbx.sae-reporting@health.mil): type and date of delivery, Apgar scores, the health status of the mother and child, and the child's sex, head circumference, gestational age at delivery, length, and weight. Pregnancy complications and/or abnormalities should be reported including any premature terminations. A pregnancy is reported as an AE or SAE only when there is suspicion that the investigational product may have interfered with the effectiveness of contraception or there was a serious complication in the pregnancy including a spontaneous abortion or an elective termination for medical rationale. Otherwise, pregnancy will not be categorized as an AE.

9.13.13 Reporting to the Drug Manufacturer

All SAEs, AESIs, SUSARs, UPIRTSOs, and pregnancies will be reported to the drug manufacturer within the same reporting period as required of reporting to regulatory authorities via the pharmacovigilance email reporting address, resilientpharma@mmsholdings.com. For SAEs and AESIs not required to be reported in an expedited manner to regulatory authorities, the PI shall provide notice to the drug manufacturer within 15 calendar days of awareness of the event via the pharmacovigilance email reporting address, resilientpharma@mmsholdings.com.

Other data that will be reported to Resilient Pharmaceuticals includes:

- Concomitant medications and psychiatric medication history

- Heart rate, blood pressure, and body temperature results
- C-SSRS results

9.13.14 Interruptions and Arrangements Due to Any Unforeseen Emergency

This clinical trial may be interrupted by an unforeseen emergency (e.g., a global pandemic). Accommodations may be required for study continuation and participant and study site staff safety due to this emergency or any other unforeseen emergency in the future. The following accommodations in the protocol will be allowed, captured, and noted as deviations related to unforeseen emergencies:

- Integration Sessions may be conducted by telemedicine
- Delaying the start of medication tapering after enrollment and the subsequent Intervention Cycle
- Delaying Dosing Sessions and associated Integration Sessions
- Delaying Independent Rater and Clinician-Administered assessments
- Use of prohibited medications or initiation of new therapy for participants with significant study delays, which will be reviewed by the study team before each Dosing Session and re-tapered prior to resuming Intervention Cycle per Section 6.7 Concomitant Medications.

For any participant with an unforeseen medical illness (e.g., Coronavirus Disease 2019), continued trial participation after full recovery of the disease may be appropriate after discussion between the study physicians and Independent Safety Monitors on a case-by-case basis.

9.13.15 Noncompliance

Noncompliance with the protocol, Good Clinical Practice (GCP), and written procedures that have the potential to significantly affect human participant protection or data reliability will constitute a reportable event. In circumstances in which the IRB determines that a deviation constitutes an unanticipated problem involving risks to participants or others or the deviation resulted from serious or continuing noncompliance, the investigator will be required to perform a root cause analysis and submission of a Corrective Action Plan to the IRB for review. All corrective actions will be documented and become a part of the regulatory file along with the report.

9.14 Statistical Analyses

9.14.1 General Considerations

Full details of statistical analyses including planned tables, figures and listings, hypotheses to be tested and hierarchical testing procedures are described in the Statistical Analysis Plan (SAP). The SAP will be developed and finalized before database lock. The final analysis will be performed after all study participants have completed their final study visit and the database is locked. Statistical significance will be determined using a significance level of 0.05. Below is a summary of planned statistical analyses of the primary, secondary, and safety endpoints.

Primary and secondary efficacy and exploratory analyses will be performed on the modified intent-to-treat (mITT) population of participants who completed at least one treatment session and had at least one post-baseline outcome assessment.

Safety analyses will be done on the safety population of all randomized participants who received a study drug.

Per-protocol analyses will be done on the subset of participants who met mITT criteria and had no major protocol deviations.

9.14.2 Primary Outcome Analysis

Primary analyses will evaluate the past month CAPS-5-R total symptom severity score change from baseline to short-term (T2: 14±3 weeks after baseline CAPS-5-R) follow up as the primary outcome. Mixed models for repeated measures (MMRM) with unstructured covariance matrices (or other covariance structure as appropriate) will be used to estimate the treatment effect of full-dose MDMA-AT versus low-dose MDMA-AT at short-term (T2) and long-term (T3: three months after the final Dosing Session) follow up visits. Model terms will include a random effect for participant and fixed effects of treatment, visit (categorical), and their interaction with baseline CAPS-5-R total symptom severity score as a covariate.

9.14.3 Secondary Outcome Analysis

Maintained differences and durability of treatment efficacy between treatment groups on CAPS-5-R change from baseline to T3 will be tested as a secondary outcome in the MMRM. Type I error will be controlled with hierarchical testing where only after rejection of the null hypothesis for the primary outcome (treatment differences at T2) would the secondary outcome (treatment differences at T3) be tested. Treatment effects will be estimated at each post-baseline visit using least square means for CAPS-5-R changes compared by treatment group with contrast t-tests.

Secondary analyses will also include estimated mean differences between treatment groups with 95% confidence intervals in functional disability (WHODAS 2.0) from baseline to primary endpoint using a generalized linear mixed model (GLMM) or similar modeling approach.

Durability in between group differences by extending the GLMM or similar approach to include interactions between baseline, T2, and T3 and treatment group on functional disability (WHODAS 2.0). Statistical significance will be set at the conventional level of $p \leq 0.05$ with outcomes at each prespecified time point reported.

The number of simultaneously overlapping support events will be described as counts by the number of simultaneous events for each treatment arm and overall.

9.14.4 Other Analyses

Exploratory analyses as well as analyses of other laboratory measures, scales, and surveys will be performed as detailed in the SAP.

9.14.5 Safety Analyses

The Protocol Safety Review Team (PSRT) will review all AEs (including SAEs and AESIs) on a regular and expedited basis. The function of the PSRT and the types of safety analyses it will conduct is further detailed in Section 11.5.3 Protocol Safety Review Team and Periodic Data Review.

Cardiac and hepatic safety and AEs will be reported with descriptive statistics (e.g., counts and percentages with 95% confidence intervals or means with standard deviations) and compared between treatment groups at each visit using traditional bivariate tests. ΔQTcMax will be compared using two-sample t-tests and the upper bound of the 95% confidence interval for the group mean difference (full-dose MDMA vs low-dose MDMA) interpreted in relation to a clinically relevant difference of >10 milliseconds.

1. Describe differences in events of ΔQTcMax > 60 ms at each dosing session by treatment group using frequencies and proportions.
2. Describe differences in events of ΔQTcMax > 500 ms at each dosing session by treatment group using frequencies and proportions.
3. Describe differences in number of arrhythmias, overall and by arrhythmia type/severity, during each dosing session by treatment group using median and interquartile range.
4. Describe changes in vital signs (systolic and diastolic blood pressure, heart rate, and body temperature) from pre-IMP administration to 2 hours and 4 hours post-dosing and end of each dosing session. Differences between treatment groups can be assessed using means and standard deviations or medians and interquartile ranges
5. Continuous ALT, AST and ALP and total/direct/indirect bilirubin will be described before and after each dosing session by group using means and standard deviations or medians and interquartile ranges.
6. Describe counts of liver injury indicated by ALT and AST by treatment group using frequencies and proportions.
7. Describe counts of close observation for liver injury indicated by ALT and AST by treatment group using frequencies and proportions.
8. Describe counts of discontinued enrollment among those with close observation for liver injury after each dosing session by treatment group using frequencies and proportions
9. Continuous sodium and potassium levels will be described before and after each dosing session by group using means and standard deviations or medians and interquartile ranges.
10. Describe counts of AEs by maximum severity across both study arms including during and after each dosing session using frequencies and proportions.
11. Describe counts of AEs by maximum severity by treatment arm and categorized as leading to discontinuation of IMP, death or hospitalization, continuing at primary endpoint, or continuing at secondary endpoint using frequencies and proportions.
12. Describe counts of TEAEs by treatment arm using frequencies and proportions.
13. Describe counts of TEAEs by maximum severity reported during a dosing session and the following days after IMP administration (1 day, 3-4 days) by treatment arm using frequencies and proportions.
14. Describe counts of SAEs by treatment arm using frequencies and proportions.
15. Describe counts of positive or serious ideation and suicidal behavior, as measured by the C--SSRS, by treatment arm using frequencies and proportions.

16. Describe counts of illicit substance use by treatment arm as measured by DUQ using frequencies and proportions.
17. Describe counts of simultaneous support events overall, by treatment arm, and by minimum monitor training level required per event.
18. Describe counts and nature of simultaneous dosing support events categorized by Emergent, Urgent, or Routine Therapist events and Emergent, Urgent, or Routine Participant events.
19. Describe time between therapist-initiated Support Event requests and the supporting monitor entering the room by treatment arm using means and standard deviations or medians and interquartile ranges.
20. Describe time between supporting monitor-initiated recognition of need for a support event and a supporting monitor entering the room by treatment arm using means and standard deviations or medians and interquartile ranges.
21. Describe number of support events that require ≤ 5 minutes and > 5 minutes for the supporting monitor to enter the room by treatment arm using frequencies and proportions.
22. Characterize reported barriers to a quicker response for each support event that took > 5 minutes for the supporting monitor to enter the room and all support events overall.
23. Characterize frequency per session and duration of support events per treatment arm and overall.
24. Describe the qualitative interventions that were provided by the supporting monitor during a support event by treatment arm.
25. Describe the corresponding AEs during a support event when a non-clinical assistant monitor temporarily monitors participants during low-risk support events by treatment arm.
26. Describe counts of a clinical assistant monitor needing to enter the room during a support event when a non-clinical assistant monitor temporarily is monitoring participants for low-risk support events by treatment arm.
27. Describe counts of meeting modified CAM discharge criteria at the planned end of the dosing session by treatment arm using frequencies and proportions.
28. Describe time from planned end of dosing session to discharge using means and standard deviations or medians and interquartile ranges.
29. For each discharge criterion, describe counts of participants who did not meet the discharge criterion at the planned end of the dosing session by treatment arm using frequencies and proportions. Describe the number of discharge criteria not met per participant at the planned end of the dosing session by treatment arm using medians and interquartile ranges.

9.14.6 Interim Analysis

No formal interim analyses are planned for this study. Aggregated data collected to-date may be reviewed by the Clinical Research Associate (CRA) or Independent Safety Monitor (ISM) as described by the clinical monitoring plan.

9.15 Sample Size Determination

The target sample size of 43 participants per treatment arm (86 randomized participants total) will give > 80% power (two-sided alpha=0.05) to detect Cohen's d=0.7 for comparison of

changes in CAPS-5-R between groups, conservatively assuming up to 20% dropout in each arm and with the detectable effect size similar to those reported in previous MDMA trials in patients with PTSD.[3,4] Complimentary simulated power calculations for a linear mixed model revealed similar sample size requirements at an equivalent effect size. Safety, secondary and exploratory analyses will not be formally powered; rather, estimates and their confidence intervals will be reported, and their potential clinical relevance described.

9.16 Data Repositories

All data supporting published manuscripts will be shared with the research community through data uploads to the Harvard Dataverse data repository.

10 Legal and Ethical Considerations Specific to Military Populations

Legal considerations for conducting MDMA-AT for SMs are governed by multiple federal statutes and military-specific regulations.[8] This study is designed to comply with all relevant laws, regulations, and policies to ensure that participation by SMs is lawful, ethical, and consistent with DoD directives.

10.1 Authority and Regulatory Compliance

This study is authorized under Section 723 of the 2024 NDAA, which permits the DoD to study psychedelic-assisted therapies, including MDMA-AT, in SMs diagnosed with PTSD or TBI.[5] Research involving Schedule I substances in military populations must follow Army Regulation (AR) 40-7, which outlines the legal and ethical prerequisites for such studies.[252] All necessary regulatory approvals—including from the IRB, Office of the Surgeon General, and relevant command authorities—have been obtained or will be secured prior to enrollment of any participant.

10.2 Legal Use vs. Illicit Use

Participation in this protocol constitutes a legally sanctioned use of MDMA under an active IND application with the FDA. Under AR 600-85, legitimate use of Schedule I substances in approved clinical settings is not considered illicit.[253] The participant's command will notify the Medical Review Officer (MRO) of their enrollment in this protocol so that the MRO may, in turn, flag any positive urine drug screens for MDMA up to 5 days after each Dosing Session to ensure appropriate interpretation and classification as authorized use.[253]

These procedures ensure that a positive result on a routine drug test will not be misclassified as unauthorized or punitive. Participants are educated about the boundaries of legal use, including that use of MDMA outside the context of this protocol constitutes a violation of the Uniform Code of Military Justice and subjects them to any associated punitive actions.[254]

10.3 Security Clearance and Personnel Reliability

Receiving MDMA under this protocol, with command approval and proper documentation, does not constitute disqualifying behavior for the purposes of security clearance maintenance or personnel security evaluations under SEAD 4,[255] DoD Manual 5200.02,[256] or DoD Instruction

5200.02.[257] Participation in IRB-approved medical research does not trigger automatic revocation of security clearance, provided the use is legal and medically supervised.[258] Furthermore, if the study intervention results in clinical improvement, participants may reduce the risk of losing security clearance status that had previously been jeopardized due to mental health conditions.[259]

Service members holding Sensitive Compartmented Information (SCI) or Special Access Program access will be counseled on any additional reporting requirements, provided with additional study documentation to provide their security manager, and advised to consult with their security manager as needed.[259]

Service members holding SCI clearance will be required to inform their Special Security Officer of their involvement in this trial prior to study enrollment.

Service members holding a Special Access Program clearance will be required to obtain pre-clearance for study participation in writing from their Program Security Officer prior to study enrollment.

10.4 Human Subject Protections and Prohibition of Coercion

All research involving service members must comply with 10 U.S.C. §980 and DoD Instruction 3216.02, which prohibit coercion and mandate informed consent.[260] To safeguard voluntariness, recruitment is conducted independently from the participant's chain of command. No command member may coerce, suggest, or imply that participation is expected or advantageous. Participants are assured that declining or withdrawing from the study will not negatively affect their duty assignments, career progression, medical care, or benefits.

The protocol's consent process includes detailed education on rights, risks, benefits, and protections specific to military status. Participants must demonstrate comprehension and freely sign the consent form before initiating any study procedures.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify the participants in this study in any action or suit unless the participant gives explicit written permission. The research team also cannot provide them as evidence unless participant gives explicit written permission. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

11 Regulatory, Ethical, and Study Oversight Considerations

11.1 Oversight of Schedule I Substances

All MDMA used in this study is pharmaceutical-grade and manufactured, stored, and administered in compliance with current Good Manufacturing Practice requirements and in accordance with Drug Enforcement Administration (DEA) Schedule I regulations.[261] The WRNMMC Investigational Pharmacy will maintain secure storage and inventory tracking. Drug accountability logs will be maintained and monitored per 21 CFR Part 312 and AR 40-7

guidelines.[251,252] Only authorized personnel with appropriate DEA registration and command approval may access or administer the investigational product.

11.2 Ethics Review

The protocol is based on adequately performed laboratory and animal experimentation and will be conducted under an Institutional Review Board-approved protocol. The study is to be conducted by scientifically and medically qualified persons. The IRB will determine whether the benefits of the protocol are in proportion to the risks. The rights and welfare of the participants will be respected, the physicians conducting the study will ensure that the hazards do not outweigh the potential benefits, the results to be reported will be accurate, participants will give their informed consent and will be competent to do so and not under duress, and all study staff will comply with the ethical principles in accordance to GCP, 21 CFR Part 50, and the Belmont Principles.

11.2.1 Protocol Modifications

All modifications to the protocol and supporting documents (informed consent, protocol-specific procedures, standard operating procedures, recruitment materials, etc.) will be reviewed and approved prior to implementation:

1. Integrated Product Team (IPT) review and approval
2. Scientific Review Board review and approval (if applicable)
3. Protocol Review Board (sponsor's representative) review and approval
4. Institutional Review Board review and approval
5. Food and Drug Administration submission

Any protocol amendment will be agreed upon and approved by the sponsor's representative, through the Protocol Review Board prior to submission to the IRB and FDA and approved by the IRB and FDA prior to implementation of said change or modification.

Any modification that could potentially increase risk to participants will be submitted to the FDA and IRB for approval prior to implementation. The informed consent document will be revised to concur with any amendment as appropriate and will be reviewed and approved with the amendment. Any participant already enrolled in the program will be informed about the revision and asked to sign the revised informed consent document if the modification directly affects the individual's participation in the program. A copy of the revised, signed, and dated informed consent document will be given to the participant. All original versions of the informed consent document will be retained in the protocol regulatory file, and a copy will be retained in the protocol regulatory file.

11.2.2 Protocol Deviations

All participant-specific deviations from the protocol (e.g., failure to return for follow-up visits or blood collection within the time indicated in the protocol) are to be documented. The principal investigator or designee will be responsible for identifying and reporting all deviations, which are defined as isolated occurrences involving a procedure that did not follow the protocol or

protocol-specific procedure. Deviations will be reported annually in the continuing review report to the IRB and, if appropriate, in the final study report.

When a deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure.

Action taken in response to the deviation and the impact of the deviation will be assessed by the PI or sub-investigator and recorded as follows.:

A major protocol deviation is any protocol deviation that adversely affects the safety or rights of a participant or scientific integrity of the study. All major protocol deviations will be reported:

- Within 24 hours of occurrence to the sponsor's clinical trial monitor or clinical trial manager, and to the IRB via email.
- Within **3 days** of occurrence to the IRB via eIRB submission.
- and Within 5 business days of occurrence to the sponsor's safety office (DHA R&D - MRDC ORA PSSO) (see Table 17).

A written report for protocol deviations (a deviation log) must be maintained and submitted by the PI to the WRNMMC IRB and sponsor per each organization's requirements and upon request.

Waivers and exemptions to protocol procedures are not allowed with the exception of immediate safety concerns and these will be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study treatment.

11.3 Ethical Conduct of the Study

This study will be conducted in accordance with all applicable federal and DoD human research protections requirements and the Belmont Principles of respect for persons, beneficence, and justice. The procedures set out in this protocol are designed to ensure that the sponsor's representative and all study personnel abide by the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP Guideline and the CFR. The principal investigator confirms this by signing this protocol and Form FDA 1572.

11.3.1 Confidentiality

In this protocol, the participant's health information will be collected and used to conduct the study; to monitor the participant's health status; to measure effects of the investigational product; to determine research results; and possibly to develop new tests, procedures, and commercial products. Health information is used to report results of research to the sponsor's representative and Federal regulators and may be reviewed during study audits for compliance with study plans, regulations, and research policies.

The IND sponsor, the sponsor's representative, the IRB, the DoD, and the FDA are eligible to photocopy and review records related to this protocol as a part of their responsibility to protect the participants of this protocol. With the approval of the PI, representatives from these organizations may witness study procedures to ensure the safety of participants.

When study information is communicated or published to support this protocol, no personal identifier will be used. The participant's identification number will be used in the event it becomes necessary to identify data specific to a single participant.

11.3.2 Compensation for Participation

Participants will be compensated for time and efforts. Compensation for each group is described in the ICFs, by each type of visit throughout the study period. Payment ranges from $20.00 to $100.00 per visit. The total amount of compensation is $630.00. If a participant needs to return to clinic for any additional unplanned visits the compensation will be $0 per visit. For all participants receiving more than $1,700 or more for taking part in a combination of research studies in one tax year, an IRS form 1099 will be issued.

If a participant chooses to leave or is removed from the study by the PI prior to its completion, they will still be eligible for the compensation related to all study visits and procedures that they have successfully completed up until that point.

11.3.3 Medical Care for Research-Related Injury

All nonexempt research involving human subjects shall, at a minimum, meet the requirement of 32 CFR 219.116(a)(6).

If a subject is injured because of participation in this protocol and is a DoD healthcare beneficiary (e.g., active duty in the military, military spouse or dependent), the subject is entitled to medical care for that injury within the DoD healthcare system, as long as the subject remains a DoD healthcare beneficiary. This care includes, but is not limited to, free medical care at DoD MTF.

If a subject is injured because of participation in this protocol and is not a DoD healthcare beneficiary, the subject is entitled to medical care for that injury at a DoD MTF; medical care charges for care at a DoD MTF will be waived. The subject is also entitled to care for that injury at other DoD (non-Army) hospitals or clinics, but such care for that injury at non-DoD MTF may be limited by time, and the subject's insurance may be billed. It cannot be determined in advance which Army or DoD medical facility will provide care. If the subject obtains care for research-related injuries outside of a DoD MTF, the subject or the subject's insurance will be responsible

for medical expenses. Transportation to and from the DoD MTF will not be provided. No reimbursement is available to subjects if they incur medical expenses to treat research-related injuries. No compensation if available for research-related injuries. Subjects are not waiving any legal rights.

11.3.4 Written Informed Consent

The PI (or designated staff) will obtain Protocol Review Board and IRB approval of the informed consent document prior to initiation of the study. The investigators or their designees will present the protocol in lay terms to individual participants with key information that may affect a participant's willingness to participate presented first.

The principal investigator or designee will solicit questions from participants on the purpose of the protocol, protocol procedures, and risks and allow the participant time to review the document. The person conducting consent will ensure that the participant understands the following principles of consent:

- Participation is entirely voluntary
- The participant may withdraw/exit from participation at any time
- Refusal to participate involves no penalty
- The participant is free to ask any questions that will allow him/her to better understand the nature of the protocol

Participants will be asked to indicate on the consent how their samples and/or data may be used in future studies.

The designated individuals will obtain a copy of the consent form signed by each participant (or legally authorized representative, if appropriate) before any study-related procedures are initiated for that participant. This signed and dated consent document will be retained as part of the study records. Each participant will receive a copy of the signed informed consent document.

Should the protocol be modified, the informed consent document must be revised to reflect the changes to the protocol. If a previously enrolled participant is directly affected by the change, the approved revision must be read, signed, and dated by the participant. A copy of the signed and dated consent must be provided to the participant.

The participant will be informed that a description of this clinical trial and the consent form template will be available on http://www.ClinicalTrials.gov, as required by U.S. law.

11.3.5 Participant-authorized Incomplete Disclosure

Overview and rationale. This study uses a Participant-authorized Incomplete Disclosure (PAID) approach. Under PAID, participants are explicitly informed during the consent process that certain non-risk-relevant study design details are intentionally described in a less specific manner, and the participant affirmatively authorizes that limited withholding as part of consent. PAID is a form of *modified informed consent* that has been discussed in the research ethics literature as ethically acceptable in defined circumstances – particularly when full disclosure would undermine scientific interpretability and the withheld information does not alter the participant's assessment of risk.[262]

PAID is used here because psychedelic-assisted therapy trials face well-recognized challenges with functional unblinding. MDMA produces distinctive subjective effects that can lead participants and study staff to infer treatment condition when exact details of study arms and dosing structure are disclosed. Such inferences can increase expectancy effects and bias outcome estimation. Matvey et al. (JAMA Psychiatry, 2025) identify modified informed consent (including incomplete disclosure) as one of the key strategies to mitigate functional unblinding in psychedelic trials, while emphasizing that such approaches should be paired with specific ethical safeguards and transparency measures.[262]

Ethical justification consistent with published guidance. As described by Matvey et al., modified consent approaches may be ethically supportable when:

1. Full disclosure would compromise the study's interpretability (e.g., by increasing functional unblinding and expectancy bias);
2. The information withheld is not material to risk (i.e., does not reasonably change a participant's assessment of risks/benefits or decision to participate);
3. Participants are transparently told up front that some non-risk-relevant details are being described less specifically, and they agree to that; *and*
4. Participants are debriefed with an opportunity to ask questions and receive the full explanation after participation (or earlier if required for purposes of safety).[262]

What is and is not being withheld. To reduce expectancy-driven bias while preserving participant autonomy and safety, the Informed Consent Document (ICD) discloses the accurate *maximum possible dose* and states the per-session dose range as 0-180 mg, whereas the true lower bound is 40 mg (true range 40-180 mg). This limited imprecision is confined solely to the *lower bound* of the disclosed dosing and is intended to help maintain blinding, because participants who experience low-intensity subjective effects may then be less able to infer assignment to a low-dose condition if, per the consented range, they believe the minimum possible dose could be 0 mg. This modification to consent targets a single specific *study design feature* (the lower bound of the dose range) rather than any *safety-relevant information*.[262]

No other aspect of the study is withheld or misdescribed, to include: known or reasonably foreseeable risks of MDMA, safety monitoring procedures, eligibility restrictions, alternatives to participation, compensation, confidentiality protections, or participants' rights. No false statements about study risks or procedures are provided.

Protection of participant autonomy and transparency during consent. Consistent with Matvey et al.'s emphasis on participant authorization, the consent discussion will explicitly state that:

1. The dose range is intentionally described with less specificity to support scientific interpretability;
2. The withheld information does not pertain to additional risks beyond those described in the ICD; and
3. Participation is voluntary and participants may withdraw at any time without penalty.

Participants will have the opportunity to ask questions and will be reminded that their decision to participate should be based on the risks, procedures, and protections that are fully described in the ICD.

Debriefing and post-participation disclosure. Participants will be offered debriefing regarding the incomplete disclosure (including the true dose range and the rationale for PAID) after the final participant completes participation to reduce cross-participant contamination or earlier if required for safety reasons. Debriefing will be documented in the research record and will include an opportunity for participants to ask questions and receive a full explanation of the design feature that was described less specifically during consent.

Monitoring whether PAID achieves its intended methodological purpose. Because the ethical rationale for PAID in this study is tied to reducing expectancy-driven bias associated with functional unblinding, the study will assess treatment expectancy at baseline and will assess blinding success for participants (and relevant study staff, as applicable) at prespecified timepoints (e.g., after Dosing Sessions and at study end). These assessments will help evaluate whether PAID meaningfully improves interpretability, consistent with the methodological focus emphasized by Matvey et al.[262]

This PAID strategy is intended to enhance scientific validity while maintaining respect for persons through explicit authorization, full disclosure of all material risks and rights, and debriefing – an approach that aligns with the ethical and methodological considerations outlined by Matvey et al.[262]

11.4 Data Protection

Participants will be assigned a unique identifier by the study team. Any participant records, datasets, or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Questionnaires will be administered via the secure web-based feature within REDCap. Participants will be emailed a secure link to access the questionnaire. Participant email will be collected so that questionnaire access can be provided via REDCap. Questionnaires are identified only by participant ID and not email address. Only authorized DCAC staff and site personnel will have access to the survey distribution feature within the database and email will not be exported for data reporting or analyses.

11.4.1 Participant Numbering

At pre-screening, each participant will be assigned a unique identification number, which will be used on all study-related documents. Participant identification numbers will include a protocol identifier (MDMA) and a sequential number (e.g. MDMA-0001, MDMA-0002, MDMA-0003).

11.4.2 Participant Recruitment

To aid in participant recruitment, we will use REDCap to collect Personally Identifiable Information demographics such as full name; email; phone number; status such as Active Duty, National Guard, Reserve, Veteran, or Civilian; and other information from potential participants pertinent to prescreening. Additionally, we will collect Protected Health Information, to include responses from self-report clinical measures such as the LEC-5, PCL-5, and SCID-5-SPQ. REDCap employs industry-standard security protocols, including encryption of data in transit and at rest, access controls, and audit logging. Access to form responses will be restricted to study personnel via secure, password-protected accounts. Data collected will be used solely for screening and contacting individuals for potential study participation, in accordance with IRB-approved procedures.

11.4.3 Data Quality Assurance

All data management activities will be conducted according to the approved study-specific Data Management and Sharing Plan (DMP).

All participant data relating to the study will be recorded on source documents and CRFs and entered into the study database by site staff. Direct entry into the study database without any source documentation is not allowed. There should always be a source document for each CRF. Source documents and completed CRFs should be reviewed at the site for completeness and accuracy before data entry when possible per site Standard Operating Procedures.

The investigator is responsible for:

- Verifying that data entries are accurate and correct by physically or electronically signing the CRFs.
- Maintaining accurate documentation (source data) that supports the information entered in the CRFs.
- Permitting study-related monitoring, audits, IRB review, and regulatory agency inspections and providing direct access to source data documents.

The sponsor, unless otherwise notified by a Transfer of Regulatory Responsibility, is responsible for the data management of this study, including quality checking of the data.

Study monitors will:

- Perform ongoing source data verification based on the study-specific clinical monitoring plan to confirm that data entered into the case report forms by authorized site personnel are accurate, complete, and verifiable from source documents
- Verify that the safety and rights of participants are being protected
- Verify that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH Guideline for GCP [ICH E6 (R2)] and all applicable regulatory requirements such as but not limited to 21 CFR Parts 50, 21 CFR 312, and FDA guidance on GCP.

11.4.4 Record Retention

Records and documents, including signed informed consent forms, pertaining to the conduct of this study will be retained by the investigator for either: 1) at least 6 years after the completion of the study or 2 years after an NDA for MDMA-AT for PTSD is FDA-approved – whichever occurs second – unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of the sponsor.

No records may be transferred to another location or party without written notification to the sponsor.

11.4.5 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents will be filed at the investigator's site. There should always be a source document for each CRF. Data reported on the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies will be explained.

Additional information that may be included as source data can be found in the DMP.

11.4.6 Pending Inspections/Issuance of Reports

The knowledge of any of the following will be reported immediately to the IRB and the DHA R&D - MRDC Office of Research Protections and the sponsor's representative through DHA R&D - MRDC ORA Quality and Compliance Office:

- Pending compliance inspection/visit by the FDA, Office for Human Research Protections (Department of Health and Human Services), or other government agency concerning clinical investigation or research
- The issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any regulatory agency, including legal or medical actions
- Any instances of serious or continuing noncompliance with the regulations or requirements

11.5 Data and Safety Monitoring

11.5.1 Study Monitoring

Study monitoring will be the responsibility of the DHA R&D - MRDC ORA. Upon successful approval of the protocol and establishment of the regulatory file, the sponsor's representative-designated clinical monitor will establish a clinical monitoring plan. To ensure that the investigator and the study staff understand and accept their defined responsibilities, the clinical monitor will maintain regular correspondence with the site and may be present during the course of the study to verify the acceptability of the facilities, compliance with the investigational plan and relevant regulations, and the maintenance of completed records. As needed, the clinical

monitor may witness the informed consent process or other applicable study procedures to assure the safety of participants and the investigators' compliance with the protocol and GCPs.

Monitoring visits by a sponsor's representative-designated clinical monitor will be scheduled to take place at the initiation of the study, during the study at appropriate intervals, and after the last participant has completed the study. A report of monitoring observations will be provided to the PI (for corrective actions), DHA R&D - MRDC ORA, and the product manager.

11.5.2 Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) is required by the sponsor. The DSMB will be composed of an independent group of experts who review safety data during the clinical trial. The DSMB will meet at least three times annually to review study data and ad hoc to evaluate the next steps during study pauses and/or to provide other recommendations regarding the safe conduct of the study as requested by the PI and/or the sponsor. The DSMB will also meet after the first 3 open-label participants have completed all of their Dosing Sessions. Unless study halt criteria are met (Section 7.6 Study Halt/Pause Criteria), all aspects of study conduct will continue unhindered during a DSMB review.

After each review of study data, the DSMB will make a recommendation to the sponsor's representative. The DSMB recommendations will be documented and provided in writing to the DHA R&D - MRDC ORA PSSO. The sponsor's representative will then decide whether to continue, modify, or suspend the study. The DHA R&D - MRDC ORA PSSO will communicate the final decision to the investigators, who in turn will notify the applicable IRB/Ethics Committees as necessary. The sponsor will notify the U.S. FDA of the final decision, as appropriate.

Ongoing monitoring of participant safety information will be performed by the study CRA and ISM as detailed in the study clinical monitoring plan.

11.5.3 Protocol Safety Review Team and Periodic Data Review

The Protocol Safety Review Team (PSRT) will review all AEs (including SAEs, and AESIs, and TEAEs) weekly and as needed. In addition, the PSRT will review aggregate safety data reports at least twice annually. At the discretion of the PI and with concurrence of the sponsor, regular PSRT meetings may be cancelled if there have not been any safety events determined to be related or possibly related to the study products and there have not been any new IP administrations prior to the date of the PSRT meeting.

The PSRT will review safety events that potentially meet study halting criteria on an expedited basis and will decide if study IP administration should be paused for participant safety purposes. The PSRT may pause study IP administration at any time but will use as a guide, based upon an abundance of data supporting the safety of the IP product, the study halting criteria listed in Section 7.6 Study Halt/Pause Criteria. The PSRT will consult the DSMB for a review of the events that lead to a study halt and make the decision to resume, amend or close the study. Study IP administration will resume only if PSRT and DSMB reviews of the events that lead to the halt result in a recommendation to permit further study IP administration. Follow-up safety visits will continue uninterrupted during an IP administration halt.

The PSRT will include the following:

- Principal Investigator or designee
- Walter Reed National Military Medical Center (WRNMMC) designated representative
- Henry M. Jackson Foundation (HJF) Consultant or designee
- Sponsor Representative or designee
- ORA Pharmacovigilance Physician (only required for reviews of safety events that meet study halting criteria)
- Independent Safety Monitor or Alternate
- Sponsor's Clinical Monitor

Additional PSRT participants may include, as needed, the following:

- Sub-/co-investigators
- Clinical research staff
- Laboratory staff
- Data management, biostatistics, and regulatory staff
- Representatives of Study Product Owners

PSRT conference calls or meetings will require, at a minimum, the participation of the PI or designee, WRNMMC/HJF Consultant or designee, a DHA R&D - MRDC ORA Pharmacovigilance Physician (only required for reviews of safety events that meet study halting criteria and after the open-label, lead-in cohort), a representative of the sponsor or designee, and the Independent Safety Monitor or Alternate Independent Safety Monitor. If both the Independent Safety Monitor and Alternate Independent Safety Monitor are not available for the PSRT conference call/meeting, the Independent Safety Monitor must provide input by email and then be immediately sent the outcome of the PSRT discussion.

The IRB and USAMRDC OHARO OHRO will be notified of the decisions taken by the PSRT based on their requirements. The DHA R&D - MRDC ORA will be responsible for safety reporting to the U.S. FDA.

No formal periodic reviews of safety analyses will be performed. Blinded participant-level or aggregate data, to include frequencies of adverse events or distributions of safety outcomes, may be reviewed by the CRA or Independent Safety Monitor as described by the clinical monitoring plan.

11.5.4 Ongoing Safety Data Review

Participant safety will be continuously monitored by the PSRT, which includes safety signal detection at any time during the study (see Section 11.5.3 Protocol Safety Review Team and Periodic Data Review).

The DSMB will also review safety data during each of the DSMB meetings that will occur at least three times annually, after the first 3 open-label participants have completed their primary endpoints or are disenrolled, and as needed (see Section 11.5.2 Independent Data and Safety Monitoring Board).

All safety data collected will be summarized and reviewed by the DSMB. Recommendations from the DSMB will be reviewed by the Sponsor's Representative for determination of next steps.

Specifically, additional data evaluation by the regulatory Sponsor's Representative will be required in the event of a potential study halt (see Section 7.6 Study Halt/Pause Criteria).

11.6 Reports and Publications

11.6.1 Annual Report to the FDA

The PI will be responsible for the preparation of a detailed annual synopsis of clinical activity, including adverse events, for submission to DHA R&D - MRDC ORA. Each annual report will summarize IND activity for the 12 months from the approval date. DHA R&D - MRDC ORA will notify the PI of the due date with sufficient time for the PI to assemble the required information.

11.6.2 Final Clinical Study Report

A final clinical study report will be prepared provided to the DHA R&D - MRDC ORA for review and approval within 6 months of study completion. The report will be prepared in accordance with the following guidelines:

- Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications
- ICH E3 Guideline "Structure and Content of Clinical Study Reports"
- The Comprehensive Table of Contents Headings and Hierarchy
- All applicable electronic Common Technical Document standards

The DHA R&D - MRDC ORA will use this report to prepare the final clinical study report for submission to the FDA.

11.6.3 Dissemination of Clinical Study Data

All data supporting published manuscripts will be shared with the research community through data uploads to the Harvard Dataverse data repository. Data sharing via this repository will occur no later than the time of publication. Participants will be unblinded and receive information about whether they received full-dose MDMA or low-dose MDMA once the database is locked after all participants have completed study enrollment. Any incidental findings may be shared with the participant's primary care provider or mental health provider(s), as appropriate. In addition, results of clinical drug trials will be provided on the publicly funded website ClinicalTrials.gov in line with the applicable regulations.

The sponsor commits to sharing, upon request from qualified scientific and medical researchers, participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the U.S. as necessary for conducting legitimate research upon review and approval of a data use proposal. Any data sent to academic researchers through the data use proposal process will be de-identified via the safe harbor method and expert determination.

Any data shared with collaborators named on the protocol outside of WRNMMC will be coded.

All sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

11.6.4 Publication Policy

Data may be published in the open medical or military literature with the identity of the participants protected. Any academic researcher desiring to publish or present data obtained during the conduct of this study will send a data use proposal to the PI and will forward the publication to the DHA R&D - MRDC ORA for concurrence prior to publication. In accordance with AR 360-1, all publications will be sent to the WRNMMC PAO and WRNMMC Department of Research Programs for review and approval prior to submission. Per Regulation, the PAO review will include an OPSEC review.

11.7 Financial Disclosure

Investigators will accurately disclose financial interests to Resilient Pharmaceuticals, the WRNMMC IRB, and any other appropriate regulatory body prior to study start, during the study if financial interests change, and 1 year after study completion. The investigators will submit necessary disclosures to the appropriate regulatory bodies.

11.8 Study and Site Closure

The Principal Investigator, Independent Safety Monitor, Sponsor’s Representative, the IRB, the USAMRDC Office of Research Protections, or the FDA may stop or suspend the use of this product at any time. Otherwise, the study will be closed after all study procedures are completed.

If a site closes, all electronic source documents will be sent to the sponsor to be filed in the sponsor’s electronic Trial Master File.

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13 Appendices

Appendix A. Roles and Responsibilities

- Principal Investigator
  - Supervises sub-investigators, co-investigators, project manager, coordinators, research assistants, and other study staff
  - Is responsible for completing informed consent process
  - Trains study staff
  - Screens individuals and reviews all of the screening tests to determine eligibility of an individual to participate in the study
  - Makes the final participant eligibility decisions or appoints a qualified designee
  - Permits auditing by the site quality unit, the USAMRDC Quality Unit, and the ORA Quality and Compliance Office
  - Assures adequate resources, time, and participant population to meet study requirements
  - Provides medical care for adverse events
  - Documents and investigates protocol deviations
  - Reports all SAEs and AESIs per protocol
  - Delegates IP accountability and administration
  - May administer IP to study participants
  - Evaluates adverse events for diagnosis, relationship, and severity
  - Ensures documentation and safety reporting
  - May function as a Lead Monitor, Supervising Monitor, Clinical Assistant Monitor, or Non-clinical Assistant Monitor, in accordance with Section 6.3.1.
- Sub-investigator
  - Assists the principal investigator in conduct of the study
  - Is responsible for completing informed consent process
  - Assists in supervising study staff
  - Reviews screening tests to determine eligibility of an individual to participate in the study
  - Screens individuals for protocol participation (physical examination and medical history)
  - Can make final eligibility decisions
  - May administer IP to study participants
  - Evaluates adverse events for diagnosis, relationship, and severity, if he or she is a qualified clinician
  - Ensures adverse events are appropriately documented and reported
  - Functions as an independent safety advocate for participants per AR 70-25 and DoD Instruction 3216.02
  - Reviews all unanticipated problems involving risk to participants or others, serious adverse events, and all participant deaths associated with the protocol and provides unbiased written reports of the events
  - At a minimum, comments on the outcomes of the event or problem and, in the case of a serious adverse events or death, comment on the relationship to participation in the

study and indicates whether he/she concurs with the details of the report provided by the study investigator.
    - May deliver psychotherapy and other clinical care within the scope of their training, license, and credentials.
    - In accordance with Section 6.3.1, may function as a Lead Monitor, Supervising Monitor, Clinical Assistant Monitor, or Non-clinical Assistant Monitor within the scope of their training, license, and credentials.

- Associate Investigator
    - Assists the principal investigator in conduct of the study
    - Is responsible for completing informed consent process
    - Reviews screening tests to determine eligibility of an individual to participate in the study
    - Screens individuals for protocol participation (physical examination and medical history)
    - Can make final eligibility decisions
    - May administer IP to study participants
    - Evaluates adverse events for diagnosis, relationship, and severity, if he or she is a qualified clinician
    - Ensures adverse events are appropriately documented and reported
    - Functions as an independent safety advocate for participants per AR 70-25 and DoD Instruction 3216.02
    - May review unanticipated problems involving risk to participants or others, serious adverse events, and participant deaths associated with the protocol and provides unbiased written reports of the events
    - At a minimum, comments on the outcomes of the event or problem and, in the case of a serious adverse events or death, comment on the relationship to participation in the study and indicates whether he/she concurs with the details of the report provided by the study investigator.
    - May deliver psychotherapy and other clinical care within the scope of their training, license, and credentials.
    - In accordance with Section 6.3.1, may function as a Lead Monitor, Supervising Monitor, Clinical Assistant Monitor, or Non-clinical Assistant Monitor within the scope of their training, license, and credentials.
    - Will likely function as a Lead or Supervising Monitor

- Project Manager
    - Manage IP accountability
    - Manage recruitment efforts
    - Oversee conduct and review of screening to determine participant eligibility
    - Oversee completion of informed consent process
    - Manage scheduling of all study activity to include all participant visit
    - Manage collection of adverse events data from study participants
    - Manage completion of case report forms
    - Train staff on protocols/protocol changes
    - Document protocol deviations
    - Ensure efficient clinic flow

  - Manage budget
  - May administer IP to study participants if within clinical scope
  - If applicable, may deliver clinical care within the scope of their training, license, and credentials.
  - In accordance with Section 6.3.1, may function as a Lead Monitor, Supervising Monitor, Clinical Assistant Monitor, or Non-clinical Assistant Monitor within the scope of their training, license, *and* credentials.
  - Will likely function as a Non-clinical Assistant Monitor. However, a project manager with the appropriate training, license, and credentials may also be a Lead, Supervising, or Clinical Assistant Monitor.

- Study Coordinator/Nurse Study Coordinator
  - May be responsible for IP accountability
  - May be responsible for completing informed consent process
  - Reviews screening tests to determine eligibility of an individual to participate in the study
  - May administer IP to study participants
  - Schedules follow-up appointments
  - Collects adverse events data from study participants
  - Coordinates all study activity to include all participant visits
  - Completes case report forms
  - Trains staff on protocols/protocol changes
  - Documents protocol deviations
  - Ensures efficient clinic flow
  - If applicable, may deliver clinical care within the scope of their training, license, and credentials.
  - In accordance with Section 6.3.1, may function as a Lead Monitor, Supervising Monitor, Clinical Assistant Monitor, or Non-clinical Assistant Monitor within the scope of their training, license, and credentials.
  - Will likely function as a Clinical Assistant Monitor (Nurse Coordinator) or Non-clinical Assistant Monitor (Study Coordinator). However, a Coordinator with the appropriate training, license, and credentials may also be a Lead or Supervising Monitor.

- Research Assistant and Other Protocol Support Staff
  - Screens study participants and compiles eligibility data for review
  - May be responsible for completing informed consent process
  - Schedules follow-up appointments
  - Collects adverse events data from study participants
  - Coordinates all study activity to include all participant visits
  - Completes case report forms
  - Documents protocol deviations
  - Ensures efficient clinic flow
  - In accordance with Section 6.3.1, may function as a Clinical Assistant Monitor or Non-clinical Assistant Monitor within the scope of their training, license, *and* credentials.

  - Will likely function as a Non-clinical Assistant Monitor (e.g., Research Assistants) or Clinical Assistant Monitor (e.g., Mental Health Technicians).

- Independent Safety Monitor
  - "Independent Safety Monitor" is equivalent to what in other studies or contexts may be described as a "Medical Monitor" or "Research Monitor."
  - Is a physician with relevant expertise
  - Primary responsibility is to provide independent and unbiased safety monitoring in a timely fashion to ensure the safety of research participants, regulatory compliance, and data integrity.
  - Required to review and provide an unbiased written report (using the Independent Safety Monitor Report Form) for all SAEs, AESIs, and participant deaths to the DHA R&D - MRDC ORA PSSO within 24 hours of their awareness of the event. The report must include, at a minimum, a brief summary of the ISM's review of the event and event outcome, relationship of the event to the investigational product, and alternate etiology if the event is deemed unrelated to the investigational product.
  - Attend PSRT meetings and provide assessments on participant withdrawals, safety data reviews and study pauses resulting from safety events that meet halting criteria.
  - Any study team member can reach out to the ISM for their services to review any potential concerns regarding study integrity or safety/rights of the participants.

- Clinical Monitor
  - Conducts qualification, initiation, interim, and closeout study site visits
  - Monitors protocol adherence – reviews informed consent, standard operating procedures, regulations, and Good Clinical Practices
  - Monitors study and regulatory documents
  - Performs source data verification of case report form data
  - Checks investigational product accountability

- Data Coordinating and Analysis Center Staff
  - Develop CDISC/CDASH-compliant CRFs
  - Develop, test and validate, implement, and maintain the study-specific database
  - Provides study-specific database end-user training to users requiring access to the study database
  - Oversees the data entry and data discrepancy management activities
  - Ensures data consistency, quality, and integrity
  - Performs Medical Dictionary for Regulatory Affairs (MedDRA) and World Health Organization Drug Dictionary (WHO-DD) coding
  - Manages and maintains the study database
  - Analyzes the verified data according to the protocol, statistical analysis plan, and any amendments in place
  - Provides documentation of statistical findings to the principal investigator for incorporation into required reports
  - Provides datasets to the sponsor as required

- Sponsor's Safety Office (DHA R&D - MRDC ORA PSSO)

- Receives safety events, reviews, follows until resolution and performs serious adverse event case processing
- Performs medical evaluation of serious adverse events and provides the final determination on relatedness and expectedness and determines expedited reporting
- Queries site for additional information as appropriate
- Reports expedited serious adverse events to regulatory authorities

Appendix B. Vitals Severity Grading Scale

Vital Sign	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Fever (oral)	38.0-38.4 °C 100.4-101.1 °F	38.5-38.9 °C 101.2-102.0 °F	39.0-40.0 °C 102.1-104 °F	> 40 °C > 104 °F
Tachycardia - beats per minute	101-115	116-130	>130	Emergency Room visit or hospitalization for tachyarrhythmia
Bradycardia* - beats per minute	50-54	45-49	<45	Emergency Room visit or hospitalization for bradyarrhythmia
Hypertension (systolic) - mmHg	140-159	160-179	≥180 without hypertensive symptoms	≥180 with hypertensive symptoms, or Emergency Room visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mmHg	90-104	105-119	≥120 without hypertensive symptoms	≥120 with hypertensive symptoms, or Emergency Room visit or hospitalization for malignant hypertension
Hypotension (systolic) - mmHg	80-89	70-79 or transient symptomatic episode resolving spontaneously	60-69 or persisting symptoms (e.g., lightheadedness, presyncope) requiring basic medical intervention (e.g., intravenous fluids)	<60 or life-threatening symptoms such as syncope, shock, or chest pain; requiring vasopressors, Emergency Room visit, or hospitalization
Hypotension (diastolic) - mmHg	50-59	40-49 or transient symptomatic episode resolving spontaneously	30-39 or persisting symptoms (e.g., lightheadedness, presyncope) requiring basic medical intervention (e.g., intravenous fluids)	<30 or life-threatening symptoms such as syncope, shock, or chest pain; requiring vasopressors, Emergency Room visit, or hospitalization

*When resting heart rate is between 60-100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.
Benign transient elevations in temperature, blood pressure, and heart rate during dosing sessions are anticipated, and vital signs adverse event grading criteria have been adjusted accordingly.

Appendix C. Common Adverse Events Grading Scale

Adverse Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Decreased appetite	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss, dehydration, or malnutrition; oral nutritional supplements indicated	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences, urgent intervention indicated
Muscle tightness	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Nausea	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity; requires outpatient intravenous hydration	ER visit or hospitalization for hypotensive shock
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self-care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Associated with electrolyte/ hemodynamic imbalance	N/A
Mydriasis	Asymptomatic or mild symptoms (e.g., slight photophobia, minor blurring of near vision)	Moderate symptoms (e.g., photophobia or blurred vision); limiting instrumental ADL	Severe, disabling symptoms (e.g., severe photophobia, significantly blurred vision); limiting self-care ADL	Mydriasis (especially if unilateral, fixed, and non-reactive) associated with signs of a life-threatening neurological event
Non-cardiac chest discomfort	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	N/A
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self-care ADL	N/A

Adverse Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods)	Inability to adequately aliment orally; tube feeding or TPN indicated	N/A
Nystagmus	N/A	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	N/A
Feeling cold	Mild or intermittent sensation of cold	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	N/A
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; limiting instrumental ADL	Severe or prolonged; limiting self-care ADL	N/A
Feeling jittery	Mild, intermittent feeling of jitteriness or inner restlessness	Moderate or persistent jitteriness; limiting instrumental ADL	Severe jitteriness, agitation, or significant distress; limiting self-care ADL	Severe agitation or delirium with associated autonomic instability or seizures
Bruxism	Mild symptoms (e.g., sense of tightness, intermittent clenching) without significant pain	Moderate, persistent clenching with associated symptoms (e.g., jaw pain, headache, muscle soreness); limiting instrumental ADL	Severe clenching, pain, or trismus (limited jaw opening); limiting self-care ADL	N/A
Restlessness	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self-care ADL	N/A
Paraesthesia	Mild symptoms with no ADL limitations	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	N/A

Adverse Event	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-Threatening (Grade 4)
Vision blurred	Intervention not indicated	Symptomatic; moderate decrease in visual acuity; limiting instrumental ADL	Symptomatic with marked decrease in visual acuity; limiting self-care ADL	Blindness
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	N/A

Abbreviations: ADL, Activities of Daily Living; ER, Emergency Room; N/A, not applicable; TPN, Total Parenteral Nutrition.

Appendix D. Lab Value Grading Scales

Lab (Normal Range)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life-Threatening (Grade 4)**
Alanine aminotransferase (ALT) (10 - 35 U/L) – **High**	39–88 (1.1–2.5x ULN)	89–175 (2.6–5.0x ULN)	176–350 (5.1–10x ULN)	>350 (>10x ULN)
Aspartate aminotransferase (AST) (10 - 35 U/L) – **High**	39–88 (1.1–2.5x ULN)	89–175 (2.6–5.0x ULN)	176–350 (5.1–10x ULN)	>350 (>10x ULN)
Alkaline phosphatase (ALP) (35 - 104 U/L) – **High**	115–208 (1.1–2.0x ULN)	219–312 (2.1–3.0x ULN)	323–1040 (3.1–10x ULN)	>1040 (>10x ULN)
Total bilirubin (0.0 - 1.2 mg/dL) – **High**	1.3–1.5 (1.1–1.25x ULN)	1.6–1.8 (1.26–1.5x ULN)	1.9–2.1 (1.51–1.75x ULN)	>2.1 (>1.75x ULN)
Direct bilirubin (0.0 - 0.3 mg/dL) – **High**	0.33–0.38 (1.1–1.25x ULN)	0.39–0.45 (1.26–1.5x ULN)	0.46–0.53 (1.51–1.75x ULN)	>0.53 (>1.75x ULN)
Albumin (3.5–5.2 g/dL) **–Low**	2.8–3.1	2.5–2.7	<2.5	--
Protein (6.6 - 8.7 g/dL) **–Low**	5.5–6.0	5.0–5.4	<5.0	--
PT (11.9–14.4 sec) **– Prolonged**	13.1–15.8 (1.0–1.10x ULN)	15.9–17.3 (1.11–1.20x ULN)	17.4–18.0 (1.21–1.25x ULN)	>18.0 (>1.25x ULN)
INR (0.80–1.10) **– Prolonged**	1.11–1.21	1.22–1.38	1.39–1.44	>1.44
Glucose (74.0–106.0 mg/dL) **– Low**	65–69	55–64	45–54	<45
Glucose (74.0–106.0 mg/dL) **– High**	107–110 (fasting)	111–125 (fasting)	126–200 (fasting)	>200 or insulin req./coma
Calcium (8.60–10.20 mg/dL) **– Low**	8.0–8.4	7.5–7.9	7.0–7.4	<7.0
Calcium (8.60–10.20 mg/dL) **– High**	10.5–11.0	11.1–11.5	11.6–12.0	>12.0
Sodium (136.0–145.0 mEq/L) **– Low**	132–134	130–131	125–129	<125

Lab (Normal Range)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life-Threatening (Grade 4)**
Sodium (136.0–145.0 mEq/L) – **High**	144–145	146–147	148–150	>150
Potassium (3.50–5.10 mEq/L) – **Low**	3.5–3.6	3.3–3.4	3.1–3.2	<3.1
Potassium (3.50–5.10 mEq/L) – **High**	5.1–5.2	5.3–5.4	5.5–5.6	>5.6
Chloride (98.0–107.0 mEq/L) – **Low**	96–97	94–95	90–93	<90
Chloride (98.0–107.0 mEq/L) – **High**	108–110	111–115	116–120	>120
Bicarbonate (22.0–29.0 mEq/L) – **Low**	20–21	18–19	15–17	<15
Bicarbonate (22.0–29.0 mEq/L) – **High**	30–32	33–35	36–40	>40
BUN (8.0–23.0 mg/dL) – **High**	23–26	27–31	>31	Requires dialysis
Creatinine (0.67–1.17 mg/dL) – **High**	1.5–1.7	1.8–2.0	2.1–2.5	>2.5 or requires dialysis
Estimated Glomerular Filtration Rate (eGFR) (≥90 mL/min/1.73 m²) – **Low**	60-89	30-59	15-29	<15 or requires dialysis
Red Blood Cell Count (RBC) (3.70 - 5.11 million cells/µL) **–Low**	3.0–3.69	2.5–2.99	2.0–2.49	<2.0
Red Blood Cell Count (RBC) (3.70 - 5.11 million cells/µL) **–High**	5.12–5.50	5.51–6.00	6.01–7.00	>7.00
Hemoglobin (11.5–15.4 g/dL) **–Low**	11.0–11.4	9.5–10.9	8.0–9.4	<8.0
Hemoglobin (11.5–15.4 g/dL) **–High**	15.5–17.0	17.1–18.5	18.6–20.0	>20.0

Lab (Normal Range)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life-Threatening (Grade 4)**
Hematocrit (35.0–45.5%) **– Low**	33–34.9	30–32.9	25–29.9	<25
Hematocrit (35.0–45.5%) **– High**	45.6–50.0	50.1–55.0	55.1–60.0	>60.0
MCV (79.5–96.8 fL) **– Low**	75–79.4	70–74.9	65–69.9	<65
MCV (79.5–96.8 fL) **– High**	96.9–105.0	105.1–115.0	115.1–125.0	>125
MCH (26.2–33.1 pg) **– Low**	24–26.1	22–23.9	20–21.9	<20
MCH (26.2–33.1 pg) **– High**	33.2–36.0	36.1–39.0	39.1–42.0	>42
MCHC (32.6–35.0 g/dL) **– Low**	31–32.5	29–30.9	27–28.9	<27
MCHC (32.6–35.0 g/dL) **– High**	35.1–36.5	36.6–38.0	38.1–40.0	>40
RDW (12.0–16.2%) **– High**	16.3–18.0	18.1–20.0	20.1–22.0	>22
WBC (3.6–10.6 x10^3/µL) **– Low**	2.5–3.5	1.5–2.49	1.0–1.49	<1.0
WBC (3.6–10.6 x10^3/µL) **– High**	10.8–15.0	15.1–20.0	20.1–25.0	>25.0
Platelet Count (162–427 x10^3/µL) **– Low**	125–140	100–124	25–99	<25
Platelet Count (162–427 x10^3/µL) **– High**	428–600	601–800	801–1000	>1000
Mean Platelet Volume (MPV, 7.0–10.9 fL) **– Low**	6.5–6.9	6.0–6.4	5.5–5.9	<5.5
Mean Platelet Volume (MPV, 7.0–10.9 fL) **– High**	11.0–12.0	12.1–13.0	13.1–14.0	>14.0
Neutrophils % (40.7–76.4%) **– Low**	35–40.6	30–34.9	20–29.9	<20
Neutrophils % (40.7–76.4%) **– High**	76.5–85.0	85.1–90.0	90.1–95.0	>95

Lab (Normal Range)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life-Threatening (Grade 4)**
Lymphocytes % (15.9–47.8%) **– Low**	13–15.8	10–12.9	7–9.9	<7
Lymphocytes % (15.9–47.8%) **– High**	47.9–55.0	55.1–65.0	65.1–75.0	>75
Monocytes % (4.5–11.8%) **– Low**	3.5–4.4	2.5–3.4	1.5–2.4	<1.5
Monocytes % (4.5–11.8%) **– High**	11.9–15.0	15.1–20.0	20.1–25.0	>25
Eosinophils % (0.3–7.1%) **– Low**	0.2–0.29	0.1–0.19	<0.1	--
Eosinophils % (0.3–7.1%) **– High**	7.2–10.0	10.1–15.0	15.1–20.0	>20
Basophils % (0.2–1.2%) **– Low**	0.1–0.19	<0.1	--	--
Basophils % (0.2–1.2%) **– High**	1.3–2.0	2.1–3.0	3.1–5.0	>5
Immature Granulocyte % (0.0–1.1%) **– High**	1.2–2.0	2.1–3.0	3.1–5.0	>5
Neutrophils Absolute (1.80–7.50 x10³/µL) **– Low**	1.5–1.79	1.0–1.49	0.5–0.99	<0.5
Neutrophils Absolute (1.80–7.50 x10³/µL) **– High**	7.51–10.0	10.1–15.0	15.1–20.0	>20
Lymphocytes Absolute (1.00–3.10 x10³/µL) **– Low**	0.75–0.99	0.5–0.74	0.25–0.49	<0.25
Lymphocytes Absolute (1.00–3.10 x10³/µL) **– High**	3.11–4.0	4.1–5.0	5.1–6.0	>6
Monocytes Absolute (0.20–0.80 x10³/µL) **– Low**	0.15–0.19	0.10–0.14	0.05–0.09	<0.05
Monocytes Absolute (0.20–0.80 x10³/µL) **– High**	0.81–1.0	1.01–1.5	1.51–2.0	>2
Eosinophils Absolute (0.00–0.50 x10³/µL) **– High**	0.51–1.5	1.51–5.0	>5.0	Hypereosinophilic

Lab (Normal Range)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life-Threatening (Grade 4)**
Basophils Absolute (0.00–0.40 x10³/µL) **– High**	0.41–0.6	0.61–1.0	1.01–2.0	>2
Immature Granulocyte Absolute (0.00–0.10 x10³/µL) **– High**	0.11–0.20	0.21–0.50	0.51–1.0	>1
nRBC % (0 /100 WBC) **– High**	1–2	3–5	6–10	>10
nRBC Absolute (0 /µL) **– High**	1–5	6–10	11–20	>20
TSH (0.270–4.200 µIU/mL) **– Low**	0.20–0.269	0.10–0.199	0.05–0.099	<0.05
TSH (0.270–4.200 µIU/mL) **– High**	4.21–10.0	10.1–20.0	20.1–50.0	>50
Free T3 (2.30–4.20 pg/mL) **– Low**	2.0–2.29	1.5–1.99	1.0–1.49	<1.0
Free T3 (2.30–4.20 pg/mL) **– High**	4.21–5.0	5.1–6.0	6.1–8.0	>8
Free T4 (0.92–1.68 ng/dL) **– Low**	0.80–0.91	0.60–0.79	0.40–0.59	<0.40
Free T4 (0.92–1.68 ng/dL) **– High**	1.69–2.0	2.01–2.5	2.51–3.0	>3.0