SPONSOR BRIEFING DOCUMENT

MIDOMAFETAMINE (MDMA) CAPSULE WITH PSYCHOLOGICAL INTERVENTION (MDMA-AT)

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING DATE: 04 JUNE 2024

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
5-HT	Serotonin
ADS	Antidepressant discontinuation syndrome
ACE	Adverse childhood experience
ADHD	Attention Deficit/Hyperactivity Disorder
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
AUDIT	Alcohol Use Disorders Identification Test
AVP	Arginine vasopressin
BP	Blood pressure
BCRP	Breast cancer resistance protein
BDI-II	Beck Depression Inventory II
BL	Baseline
BMI	Body mass index
BPM	Beats per minute
BSEP	Bile salt export pump
BSI	Brief symptom inventory
CAPS-5	Clinician Administered PTSD Scale for DSM-5
CAPS-IV	Clinician-Administered PTSD Scale for DSM-IV
CBT	Cognitive Behavioral Therapy
CFB	Change from Baseline
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
CL/F	Oral clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
COMT	Catecholamine-O-methyltransferase
COVID-19	Coronavirus disease 2019
CPGS	Chronic Pain Grade Scale
CPT	Cognitive Processing Therapy
CSA	Controlled Substance Act
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Cardiovascular
CYP	Cytochrome P450
DB	Double-blind
DBP	Diastolic blood pressure

DBT	Dialectical Behavior Therapy
DDI	Drug-drug interaction
DEA	Drug Enforcement Administration
DILI	Drug-induced liver injury
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSP-I	Dissociative Subtype of PTSD Interview
DUDIT	Drug Use Disorders Identification Test
EAT-26	Eating Attitudes Test
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EDC	Electronic data capture
EMDR	Eye Movement Desensitiziation and Reprocessing
EQ-5D-5L	EuroQol Five Dimensions Five Levels
ES	Experimental session
FDA	Food and Drug Administration
GWB	General wellbeing
HCl	Hydrochloride
HCV	Hepatitis C
hERG	human ether-a-go-go-related gene
HHA	3,4-dihydroxyamphetamine
HHMA	3,4-dihydroxymethamphetamine
HMA	4-hydroxy-3-methoxyamphetamine
HMMA	4-hydroxy-3-methoxymethamphetamine
HPQSF	Health and Work Performance Absenteeism and Presenteeism Short Form
HR	Heart rate
IASC	Inventory of Altered Self Capacities
iDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
IPF	Inventory of Psychosocial Functioning
IR	Independent rater
ISS	Integrated summary of safety
ITT	Intent-to-treat
IWRS	Interactive Web-based Randomization System
Ki	Inhibitory constant
LEC-5	Life Events Checklist for DSM 5
LS	Least squares
LSD	Lysergic acid diethylamide
LTFU	Long-term follow-up
MAOI	Monoamine oxidase inhibitor

MAPS	Multidisciplinary Association for Psychedelic Studies
MAPS PBC	MAPS Public Benefit Corporation
MDA	3,4-methylenedioxyamphetamine
MDMA	3,4-methylenedioxymethamphetamine
MDMA-AT	MDMA-assisted therapy
MDR	Multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
MEQ	Mystical Experiences Questionnaire
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
MOA	Mechanism of action
MS	Medication session
NDA	New Drug Application
NEO-PI	Neuroticism Extroversion Openness Personality Inventory
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
OATP	Organic anion transporting polypeptide
O-DEQ	Observer-rated Drug Effect Questionnaire
OL	Open label
PASAT	Paced Auditory Serial Addition Test
PBPK	Physiologically-based pharmacokinetic
PCL-5	PTSD checklist for DSM-5
PD	Pharmacodynamics
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
P-SEMS	Participant-rated Subjective Effects of MDMA Scale
PT	Preferred term
PTSD	Post-traumatic stress disorder
PVC	Premature ventricular contraction
QHP	Qualified healthcare provider
QT	Interval from Q wave to the end of T wave
QTc	QT corrected for heart rate
QTcF	Fridericia QT correction formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCFT	Rey-Osterrieth Complex Figure Test
REML	Restricted maximum likelihood
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SAP	Statistical analysis plan

SBP	Systolic blood pressure
SCS	Self-Compassion Scale
SD	Standard deviation
SDS	Sheehan Disability Scale
SE	Standard error
SERT	Serotonin transporter
SNRI	Serotonin and norepinephrine reuptake inhibitor
SOC	System organ class
SPA	Special Protocol Assessment
SRNU	Self-reported Nicotine Use
SRR	Spontaneously reported reaction
SSRI	Selective serotonin reuptake inhibitor
SUD	Subjective units of distress
$T_{1/2}$	Half-life
TAS-20	Toronto Alexithymia Scale
TEAE	Treatment-emergent adverse event
T_{max}	Time of observed maximum concentration
TSS	Total severity score
UFEC	Utilization of Facility-based and Emergent Care
US	United States
VAS	Visual analog scale
VMAT	Vesicular monoamine transporter

1 EXECUTIVE SUMMARY

1.1 Introduction

Lykos Therapeutics, Inc. (“Lykos”), formerly MAPS Public Benefit Corporation (MAPS PBC), is seeking approval for the use of midomafetamine (i.e., MDMA) capsules in combination with psychological intervention (i.e., MDMA-assisted therapy [MDMA-AT]), for the treatment of post-traumatic stress disorder (PTSD).

MDMA is not currently approved for use in any market and is considered a new chemical entity.

1.2 Background and Unmet Need

PTSD can occur after a person is exposed to death, serious injury or sexual violence and is associated with morbidity that has substantial impact on day-to-day functioning. Symptoms create long-lasting distress or functional impairment. PTSD is associated with an all-cause mortality hazard ratio of 2.41 (95% CI [2.11-2.73]) (Ahmadi et al, 2011). Family members also feel the effects of insufficiently treated PTSD. PTSD can cause fractured relationships, depression, inability to maintain employment, diminished cognitive and psychosocial functioning, and substance use disorders (Galovski & Lyons, 2004).

Lifetime prevalence rates of PTSD in the general adult population in the U.S. and Canada have been reported to range from 6.1% to 9.2% (Kessler et al, 2005; Van Ameringen et al, 2008; Koenen et al 2017; Goldstein et al, 2016). PTSD is estimated to affect approximately 13 million Americans each year, with women and disadvantaged or marginalized groups more likely to be affected (US Dept of Veteran Affairs, 2023; Goldstein et al, 2016). On average, patients experience PTSD symptoms for more than 6 years (Kessler et al, 2017) and approximately 48% of patients remain untreated (Rodriguez et al, 2003).

Evidence-based, individual trauma-focused psychotherapy is the recommended first line treatment over available pharmacologic interventions (VA/DOD, 2023; APA, 2019). However, even these effective therapies are associated with high dropout rates, poor access, and a highly variable benefit to patients (Hoge et al, 2014; Haagen et al, 2015; Najavits, 2015; Kantor et al, 2017; Lewis et al, 2020).

Clinical guidelines provide a conditional recommendation for pharmacologic treatments due to “insufficient evidence of efficacy and safety in adequately designed placebo-controlled trials”. These pharmacotherapies include two FDA-approved SSRIs for treatment of PTSD, sertraline (Zoloft®; first approved for PTSD in 1999) and paroxetine (Paxil®; first approved for PTSD in 2001), as well as another SSRI, fluoxetine, and a SNRI, venlafaxine, used off-label to treat PTSD (Apotex, 2021; Pfizer, 2021; APA, 2019). Approved PTSD medications require daily dosing for at least 12 weeks for efficacy (Apotex, 2021; Pfizer, 2021), and long-term, consistent use is generally necessary to maintain effectiveness (VA/DOD, 2023). In addition, the response rates of

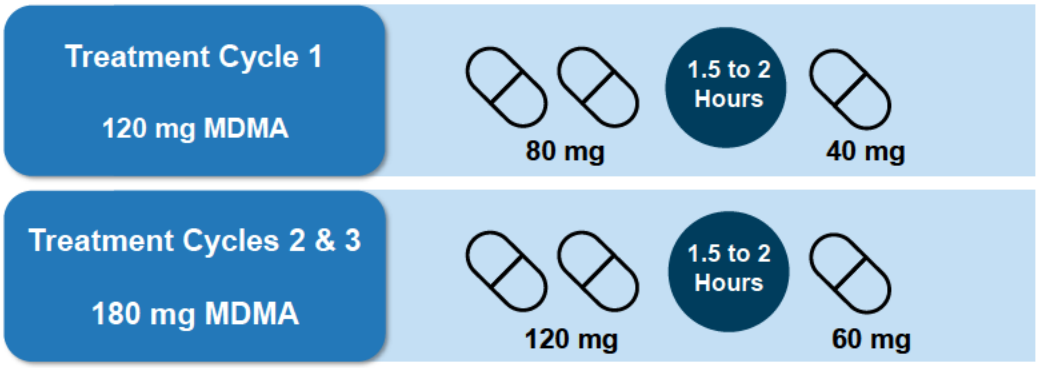
SSRIs rarely exceed 60%, and less than 20% to 30% of the patients achieve remission (Berger et al, 2009).

PTSD is an undertreated, serious, and life-threatening condition, with 40% to 60% of patients remaining symptomatic and meeting diagnostic criteria even after receiving treatment (Steenkamp et al, 2015; Bradley et al, 2005; Brady et al, 2000). There is a significant unmet medical need for an effective, well-tolerated treatment paradigm to adequately address treatment for patients with PTSD.

1.3 Product Description

MDMA (3,4-methylenedioxymethamphetamine) is an entactogen indicated for the treatment of PTSD in combination with psychological intervention in adults. It is proposed for acute single dose use (3 split dose administrations, each separated by at least 21 days; Figure 1). The drug product is formulated as an immediate release capsule for oral administration, in 2 dosage strengths (34 and 50 mg MDMA free base; equivalent to 40 and 60 mg MDMA hydrochloride [HCl]).

Figure 1: Treatment Administration



MDMA: 3,4-methylenedioxymethamphetamine
Note: All doses shown are for MDMA HCl (equivalent to the free base dosage strengths 102 and 150 mg MDMA that will be indicated in labeling).

In clinical trials, the therapeutic program was conducted utilizing a specific training manual (i.e., manualized therapy). It is intended that MDMA is used in conjunction with a specific therapeutic program consisting of preparatory psychotherapy sessions, 3 medication sessions (including psychological intervention), and follow-up integration sessions (Figure 3).

MDMA is included in a pharmacological class of drugs known as “entactogens” (Nichols, 2022). The subjective effects of this class of drug vary from classical psychostimulant or hallucinogenic effects. The prosocial effects of MDMA include enhanced sociability, empathy, and trust, while reducing defenses and fear of emotional injury, and making unpleasant memories less disturbing while enhancing communication and capacity for introspection (Bedi et al, 2014; Wardle and de Wit, 2014; Wardle et al, 2014; Carhart-Harris et al, 2015). MDMA may provide the

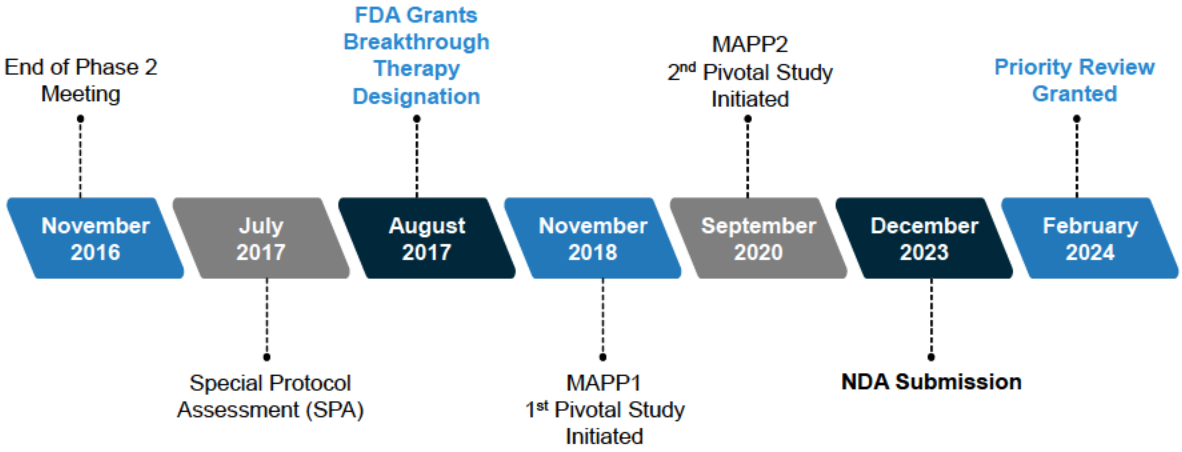
opportunity for a corrective emotional experience and cognitive processing of the trauma in the context of therapy, which may facilitate a long-term therapeutic effect.

These effects are thought to be primarily mediated by release of serotonin (5-HT) (Hysek et al, 2012; Liechti et al, 2000a) and norepinephrine (Hysek et al, 2011), and the activation of 5-HT2 receptors (Liechti et al, 2000b). Effects of MDMA are distinct from psychostimulants such as d-amphetamine and methamphetamine, which primarily activate dopamine and norepinephrine systems, with only minimal effects on serotonin (Simmler et al, 2013; Verrico et al, 2007).

1.4 Development Program

In 2001, the Sponsor opened an investigational new drug (IND) application to conduct an international series of Phase 1 to 3 clinical trials to investigate the medical use of MDMA-AT for treatment of PTSD. In 2017, the Sponsor worked with the U.S. Food and Drug Administration (FDA) to reach agreement on the design and size of the Phase 3 clinical trials through a process known as a Special Protocol Assessment (SPA) (Figure 2). Subsequently, MDMA was granted Breakthrough Therapy Designation by the FDA for treatment of PTSD based on Phase 2 clinical trial data. In December 2023, the Sponsor submitted the final sequence in a series of rolling submissions and the FDA initiated filing review of the New Drug Application (NDA) for MDMA used in combination with psychological intervention for the treatment of PTSD. In February 2024, FDA filed the application and granted Priority Review.

Figure 2: MDMA-AT Key Regulatory and Clinical Development Milestones



FDA: Food and Drug Administration; IND: Investigational New Drug; NDA: New Drug Application; SPA: Special Protocol Assessment

MDMA-AT has been studied in Phase 1, 2, and 3 trials, and is supported by safety data from the Sponsor's clinical development program in 17 clinical studies, with 427 participants exposed to MDMA (287 participants with PTSD and 140 healthy volunteers) and informed by the published literature.

1.5 Clinical Pharmacology

The assessment of clinical pharmacology is based on data from the published literature, including one study where right of reference was obtained by the Sponsor, and a sponsored pharmacokinetic (PK) study on the effect of food on the relative bioavailability of MDMA in healthy volunteers. Key findings include:

- Metabolites of MDMA include the minor but active metabolite MDA and the major inactive metabolite HHMA.
- MDMA is not a substrate for intestinal or hepatic transporters and is not actively transported into tissues.
- MDMA is primarily eliminated by hepatic metabolism with minimal renal contribution.
- MDMA is a strong CYP2D6 inhibitor and has been shown to perpetrate PK drug interactions due to inhibition of CYP2D6.
- MDMA is also metabolized by CYP2D6, but no meaningful interactions have been described with MDMA as a victim of drug-drug interactions.
- Population PK analyses did not identify any clinically significant covariates by age, sex, race, or food consumption.
- A food effect study demonstrated that the pharmacokinetics of MDMA are bioequivalent when MDMA is administered with or without food. Absorption was delayed when administered with food.
- Onset of MDMA effects occurs 30 to 60 minutes after oral administration, peak effects occur 75 to 120 minutes post-drug, and the duration of effects lasts from 3 to 6 hours.

1.6 Pivotal Phase 3 Studies: MAPP1 and MAPP2

1.6.1 Study Design

The two Phase 3 pivotal trials, MAPP1 and MAPP2, were confirmatory, randomized, double-blind, placebo-controlled, multi-site studies conducted sequentially to evaluate safety and efficacy in participants with severe PTSD (MAPP1) and at least moderate PTSD (MAPP2) which utilized the same design (Figure 3). Placebo with identical psychotherapy (as was provided to the MDMA group) was chosen as the comparator for Phase 3 with Agency consultation after consideration of other potential controls. The underlying therapeutic program was administered to both treatment arms.

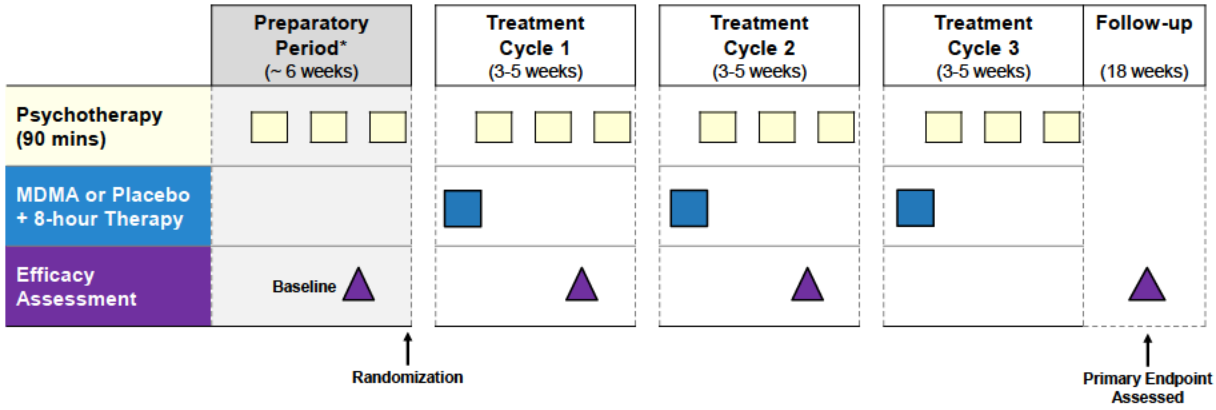
Phase 3 studies began with a screening and preparation phase including 2 preparatory sessions and a washout period for participants taking any prohibited psychiatric medication. Prohibited medications included any used for the treatment of PTSD (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], cannabis) and any medication with significant serotonergic effect

(e.g., St. John's Wort). After washout, a Baseline Clinician-Administered PTSD Scale (CAPS-5) assessment was conducted, followed by a third preparatory session.

During the treatment phase, 3 treatment cycles were planned, each lasting 3 to 5 weeks and including an 8-hour medication session and 3 weekly 90-minute integration sessions. Participants took 120 mg split dose at the medication session in treatment cycle 1 and 180 mg split dose at the medication sessions in treatment cycles 2 and 3. The total duration of the treatment course was approximately 12 weeks.

Central nervous system (CNS)-active drugs with rapid onset of psychoactive effects are often functionally unblinding and thus, present a challenge in the design of double-blind studies (FDA, 2023). Several methods were implemented in agreement with FDA to ensure the Phase 3 pivotal trials were adequate and well-controlled, including the use of a blinded, centralized independent rater (IR) pool for all efficacy endpoints, consistent therapeutic methodology, and an unblinded Independent Data Monitoring Committee (iDMC). Additional details on mechanisms implemented to maintain blinding and minimize bias are discussed in Section 6.2.3.

Figure 3: MAPP1 and MAPP2 Clinical Design



MDMA: 3,4-methylenedioxymethamphetamine
*1:1 randomization and baseline endpoint evaluations were conducted following first independent rater (IR) video assessment

At least 6 months after the last medication session, eligible participants were strongly encouraged to participate in a separate observational long-term follow-up (LTFU) study, MPLONG to evaluate durability of the treatment effect (Section 6.8).

1.6.2 Endpoints

The following efficacy endpoints were included in both pivotal Phase 3 studies (MAPP1 and MAPP2):

Primary Endpoint: Mean change in CAPS-5 total severity score (TSS) from Baseline to Week 18

Key Secondary Endpoint: Mean change in clinician-rated functional impairment, as measured by the Sheehan Disability Scale (SDS) from Baseline to Week 18

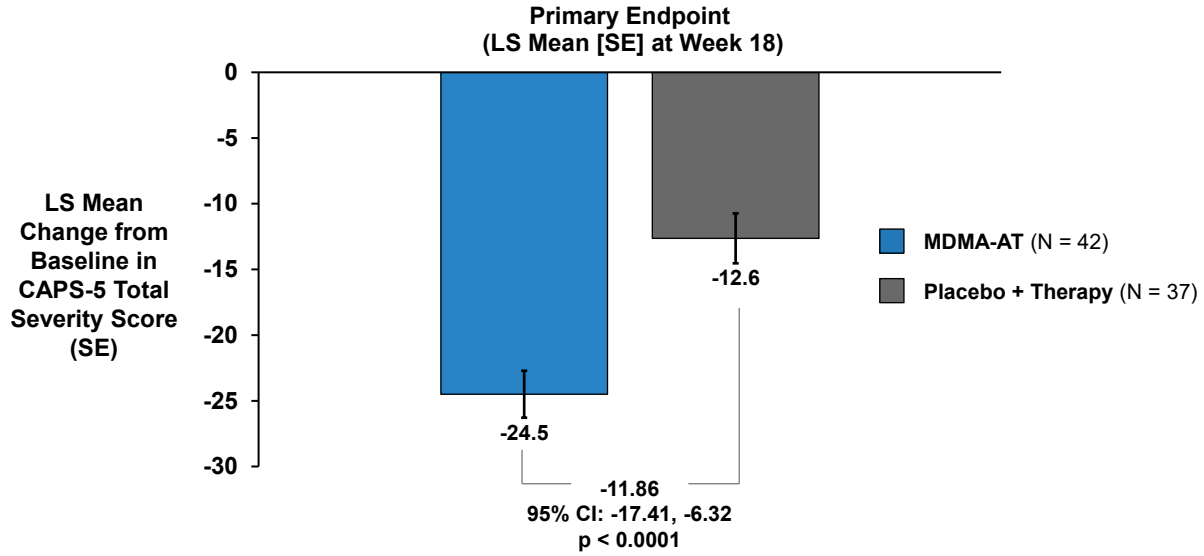
The primary (Section 6.3.1) and key secondary (Section 6.3.2) efficacy measures utilized in the pivotal Phase 3 studies are standard measurements, widely used in clinical trials and generally recognized as reliable, accurate, and relevant for the assessment of participants with PTSD.

1.7 Efficacy Findings

1.7.1 Primary Endpoint Results

In MAPP1, both treatment groups demonstrated clinically meaningful improvements in PTSD symptoms, as assessed by the least squares (LS) mean change from baseline in the CAPS-5 TSS. The changes from baseline were 24.5 points and 12.6 points in the MDMA-AT and placebo with therapy groups, respectively. The difference between groups (11.86) was statistically significant ($p < 0.0001$) and favored the MDMA-AT group (Figure 4).

Figure 4: MAPP1 Primary Endpoint: Clinically Meaningful Improvement with Statistically Significant Difference between Groups in CAPS-5 TSS (mITT)

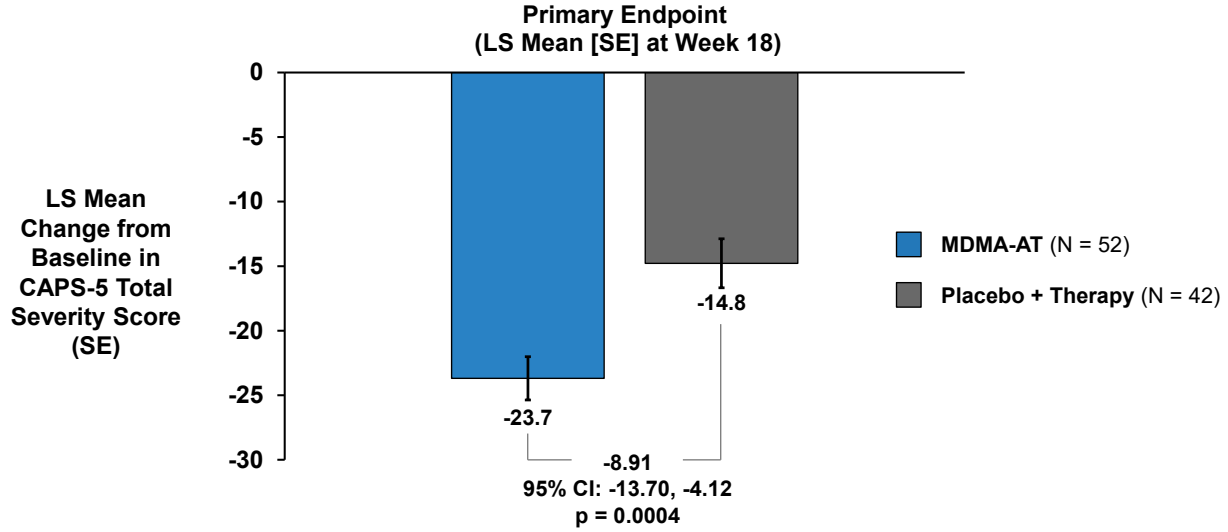


CAPS-5: Clinician-Administered PTSD Scale for DSM-5; LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SE: standard error
Note: Bars indicated ±1 SE
MMRM analysis uses all mITT participants.
Source: MAPP1 CSR Amendment, Table 14.2.1.1.1

In MAPP2, both treatment groups demonstrated clinically meaningful improvements in PTSD symptoms, with LS mean reductions in CAPS-5 TSS of 23.7 points and 14.8 points in the MDMA-AT and placebo with therapy groups, respectively. The difference

between groups (8.91) was statistically significant (p = 0.0004) and favored the MDMA-AT group (Figure 5).

Figure 5: MAPP2 Primary Endpoint: Clinically Meaningful Improvement with Statistically Significant Difference between Groups in CAPS-5 TSS (mITT)



CAPS-5: Clinician-Administered PTSD Scale for DSM-5; LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SE: standard error
Note: Bars indicated ±1 SE
MMRM analysis uses all mITT participants.
Source: MAPP2 CSR, Table 14.2.1.1.1

1.7.2 Responder Analyses of Primary Endpoint

In MAPP1, a higher proportion of participants in the MDMA-AT group compared to the placebo group were classified via their CAPS-5 TSS at Week 18 as Responders (88.1% vs. 62.2%). Treatment differences were also observed for the more conservative CAPS-5 categories of Loss of Diagnosis (66.7% vs. 32.4%), and In Remission (33.3% vs. 5.4%) (Figure 14).

In MAPP2, a higher proportion of participants in the MDMA-AT group compared to the placebo group were classified via their CAPS-5 TSS at Week 18 as Responders (86.5% vs. 69.0%). Treatment differences were also observed for the more conservative CAPS-5 defined categories of Loss of Diagnosis definition (71.2% vs. 47.6%), and In Remission (46.2% vs. 21.4%) (Figure 19).

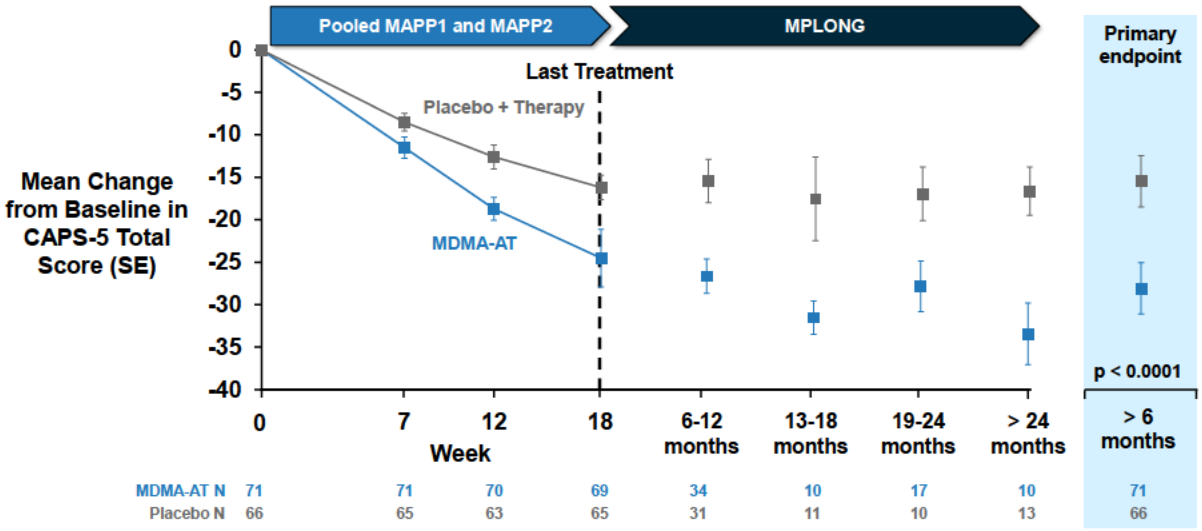
1.7.3 Long-Term Follow-Up Study Results

Eligible participants were strongly encouraged to participate in a separate LTFU study, MPLONG, in which the follow-up assessments were to occur at least 6 months after the last treatment in the parent study (Section 6.8). This study collected follow-up data, including one additional CAPS-5 assessment, at least 6 months after the last

medication session in a parent study (timing of the LTFU visit varied from 6 months to >24 months). No study drug or therapy was administered in this study.

The primary endpoint CAPS-5 TSS data in this LTFU study demonstrated a maintenance of the separation between the treatment groups. Figure 6 shows the separation between treatment groups at primary endpoint and that this separation was maintained regardless of time to LTFU.

Figure 6: MPLONG Change from Phase 3 Parent Study Baseline in CAPS-5 Total Severity Score (Effectiveness Subset; MAPP1 and MAPP2) – Time Since Treatment Subgroups



CAPS-5: Clinician Administered PTSD Scale for DSM-5; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; SE: standard error
Effectiveness subset: all participants who completed a follow-up PTSD endpoint assessment
For the follow-up duration categories, each participant is including in one visit window only (e.g., 6-12 months, 13-18 months, 19-24 months, >24 months). The sum of the numbers of participants in each of the follow-up duration categories in the placebo group is 65 as one participant with a follow-up duration of 1 day < 6 months was not included in the 6-12 month visit window.
Note: p-values shown are nominal and added for descriptive purposes.
Source: MPLONG CSR Interim, Table 14.2-2.3

Consistent with the primary endpoint responder analysis results in MAPP1 and MAPP2, a higher proportion of participants in the MDMA-AT group compared to the placebo group still met the definition of Responder, Loss of Diagnosis, and Remission at LTFU (Figure 26).

These data provide evidence of durability of the treatment effect after acute treatment with MDMA-AT at ≥ 6 months following the last medication session in the parent study.

1.8 Safety Findings

The focus of safety in this briefing document is on pooled data from the Phase 3, placebo-controlled MAPP1 and MAPP2 studies (Pooled Phase 3; Safety Set), as they provide the best assessment of the safety profile of MDMA-AT in comparison to placebo

in blinded studies, in the target patient population, who have been treated with the intended dosing regimen.

The overall summary of adverse events (AEs) in the Phase 3 pool was generally similar across treatment groups (Table 1). There were no deaths and no participants in the MDMA-AT group had a serious adverse event (SAE). A higher proportion of participants reported treatment-emergent adverse event (TEAEs) leading to discontinuation in the placebo group (5.3% [n = 5]) compared to the MDMA-AT group (1.0% [n = 1]). Most of the participants experienced TEAEs within the 2 days of dosing.

Table 1: Overall Summary of Adverse Events (Pooled Phase 3; Safety Set)

Number of Participants	MDMA-AT N = 99 n (%)	Placebo + Therapy N = 95 n (%)
TEAEs	99 (100.0)	93 (97.9)
Severe TEAEs	9 (9.1)	9 (9.5)
TEAEs with first occurrence on Day 0, 1, or 2 relative to medication session	98 (99.0)	85 (89.5)
TEAEs leading to discontinuation of IMP	1 (1.0)	5 (5.3)
Treatment-emergent SAEs	0 (0.0)	2 (2.1)
AEs leading to death	0 (0.0)	0 (0.0)

AE: adverse event; IMP: investigational medicinal product; IMP: investigational medicinal product; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; SAE: serious adverse event; TEAE: treatment-emergent adverse event
TEAEs leading to IMP discontinuation were identified based on the action taken with study treatment of drug withdrawn, or if not available, "discontinued medication session."
Percentages are calculated using the number of participants in each treatment group (N) as the denominator.
Source: ISS Table 14.3.1.3.1.

The 3 most common TEAEs in the MDMA-AT group were headache (MDMA-AT: 71.7%; placebo: 57.9%), muscle tightness (MDMA-AT: 59.6%; placebo: 20.0%), and decreased appetite (MDMA-AT: 43.4%; placebo: 10.5%) (Section 7.3.1). The majority of reported AEs were mild to moderate in severity and resolved within 2 days post-dose (Sections 7.3.2 and 7.3.3).

In the MDMA-AT group (99 participants), 1 participant reported a severe TEAE of depression that led to study drug discontinuation. In the placebo group (95 participants), a total of 5 participants discontinued due to TEAEs: mild suicidal ideation, moderate suicidal ideation, insomnia, and abdominal pain (reported in 1 participant each) and 1 participant who reported 3 TEAEs leading to discontinuation (panic attack and 2 TEAEs of suicide attempt, one moderate and one severe in severity) (Table 24).

MDMA-AT was generally safe and well-tolerated in the Sponsor's development program. The Sponsor has proposed mitigation strategies for the identified risks of MDMA-AT, both observed and theoretical (Section 7.7). These planned strategies have been integrated into a safe-use framework currently under development by the Sponsor in consultation with the FDA (Section 8.2). Stakeholders in this paradigm include prescribers, qualified healthcare providers (QHPs, i.e., therapists) and patients. This

framework is intended to ensure adequate systems are established to manage identified and emergent risks associated with MDMA-AT in the post-marketing setting.

1.9 Benefit-Risk Summary

PTSD is an undertreated, serious condition that may be life-threatening. There is a substantial unmet medical need for an additional effective treatment with a positive benefit-risk profile for PTSD. The Sponsor's development program was informed by an extensive body of literature and evaluated the safety and efficacy of an acute regimen of MDMA-AT for the treatment for PTSD.

Evidence of efficacy for MDMA-AT includes 2 positive adequate and well-controlled Phase 3 studies. Treatment with MDMA-AT resulted in statistically significant and clinically meaningful improvements in PTSD symptom severity with additional statistically significant, supportive evidence of clinically meaningful improvement in functional impairment due to PTSD.

MDMA-AT was generally safe and well-tolerated in the Sponsor's development program. The Sponsor is working with the FDA to establish a safe-use framework to manage the identified risks, both observed and theoretical. Mitigation strategies include a Risk Evaluation and Mitigation Strategy (REMS) program with a patient registry, warnings and precautions and recommendations for the prescribing physician in the label, post-marketing surveillance and risk assessment, QHP education (MDMA-AT Training Program), single dose packaging, and Drug Enforcement Administration (DEA) compliant distribution.

MDMA-AT has the potential to provide a substantial treatment benefit to patients who suffer from PTSD. The identified and potential risks can be mitigated by the measures described above. Overall, these data demonstrate that the benefits exceed the risks of MDMA-AT for patients with PTSD. If approved, MDMA-AT will provide patients suffering from PTSD a novel treatment paradigm that engages them in a psychological intervention while offering the benefits of an acute pharmacological intervention. There remains an unmet medical need for effective and well-tolerated treatments for PTSD, a condition representing a wide-spread and serious risk to public health.

2 BACKGROUND ON POST-TRAUMATIC STRESS DISORDER (PTSD)

Summary

- PTSD can occur after a person is exposed to death, serious injury or sexual violence and is associated with morbidity that has substantial impact on day-to-day functioning. Symptoms create long-lasting distress or functional impairment.

- Symptoms include persistently re-experiencing the traumatic event (e.g., flashbacks, nightmares), avoidance of trauma-related stimuli, negative thoughts or feelings (e.g., negative affect, feeling isolated), and trauma-related arousal and reactivity (e.g., irritability, aggression, difficulty sleeping, heightened startle reaction).
- Insufficiently treated PTSD frequently progresses and may become chronic or be associated with serious suicidal ideation and behavior, negatively impacting families and caregivers.
- A substantial proportion of patients with PTSD lack access or are unable to tolerate or fail to respond to available therapy (both drug and non-drug therapies).
- There is a significant unmet medical need for an effective, well-tolerated, treatment paradigm to adequately address treatment for patients with PTSD.

2.1 Overview of PTSD

PTSD can occur after a person is exposed to death, serious injury or sexual violence and is associated with morbidity that has substantial impact on day-to-day functioning. Symptoms create long-lasting distress or functional impairment. Symptoms include persistently re-experiencing the traumatic event (e.g., flashbacks, nightmares), avoidance of trauma-related stimuli, negative thoughts or feelings (e.g., negative affect, feeling isolated), and trauma-related arousal and reactivity (e.g., irritability, aggression, difficulty sleeping, heightened startle reaction). Insufficiently treated PTSD frequently progresses, and may become chronic or be associated with serious suicidal ideation and behavior (Stanley, 2021; APA, 2019; Panagioti et al, 2012; Sareen et al, 2006). Family members also feel the effects of insufficiently treated PTSD. Spouses are more likely to develop anxiety and depression, children are more likely to have behavioral problems, and violence is more likely to erupt in the home (Galovski and Lyons, 2004). PTSD is associated with an all-cause mortality hazard ratio of 2.41 (95% CI [2.11-2.73]) (Ahmadi et al, 2011).

PTSD can cause fractured relationships, depression, inability to maintain employment, diminished cognitive and psychosocial functioning, and substance use disorders. As a result, it is associated with high-cost healthcare utilization ($34.9 billion in inflation-adjusted charges for hospitalizations [2002-2011]) and decreased quality of life (Haviland et al, 2016; Dorrington et al, 2014; Tarrier and Gregg, 2004; de Jong et al, 2003; Thabet and Vostanis, 1999). PTSD is also a significant source of disability among veterans and total healthcare costs for both military and civilian populations (Davis et al, 2022; VA Annual Benefits Report, 2023).

Lifetime prevalence rates of PTSD in the general adult population in the U.S. and Canada have been reported to range from 6.1% to 9.2% (Kessler et al, 2005; Van Ameringen et al, 2008; Koenen et al 2017; Goldstein et al, 2016). PTSD is estimated to

affect approximately 13 million Americans each year, with women and disadvantaged or marginalized groups more likely to be affected (US Dept of Veteran Affairs, 2023; Goldstein et al, 2016). On average, patients experience PTSD symptoms for more than 6 years (Kessler et al, 2017) and approximately 48% of patients remain untreated (Rodriguez et al, 2003).

Common comorbidities of PTSD include anxiety and depression, as well as increased risk of suicide (Barbano et al, 2019; Nichter et al, 2019). PTSD is also associated with increased risk of Type 2 diabetes and cardiovascular disease (Seligowski et al, 2022; Lukaschek et al, 2013). Diagnosis with PTSD is associated with a 53% increase in incident cardiac events or cardiac specific mortality, with the risk remaining at 27% after adjusting for depression (Edmondson and von Kanel, 2017).

2.2 Current Treatment Options

There have been numerous clinical guidelines published for the treatment of PTSD (APA, 2019). Most recommend evidence-based, individual trauma-focused psychotherapy (e.g., prolonged exposure, cognitive behavioral therapy [CBT], cognitive processing therapy [CPT], and eye movement desensitization therapy [EMDR]) as first line treatment over available pharmacologic interventions (VA/DOD, 2023; APA, 2019). However, even these effective therapies are associated with high dropout rates (> 46.6%), poor access, and a highly variable benefit to patients (Hoge et al, 2014; Haagen et al, 2015; Najavits, 2015; Kantor et al, 2017; Lewis et al, 2020).

Clinical guidelines also provide a conditional recommendation for pharmacologic treatments due to “insufficient evidence of efficacy and safety in adequately designed placebo-controlled trials”. These pharmacotherapies include two FDA-approved SSRIs for treatment of PTSD, sertraline (Zoloft®; first approved for PTSD in 1999) and paroxetine (Paxil®; first approved for PTSD in 2001), as well as another SSRI, fluoxetine, and a SNRI, venlafaxine, used off-label to treat PTSD (Apotex, 2021; Pfizer, 2021; APA, 2019).

Approved PTSD medications require daily dosing for at least 12 weeks for efficacy (Apotex, 2021; Pfizer, 2021), and long-term, consistent use is generally necessary to maintain effectiveness (VA/DOD, 2023). In addition, the response rates of SSRIs rarely exceed 60%, and less than 20% to 30% of the patients achieve remission (Berger et al, 2009).

SSRI/SNRI tolerability is also major concern as adverse drug reactions associated with chronic daily treatment include sexual dysfunction/loss of libido, headaches, insomnia, decreased appetite, anxiety/feeling jittery, dizziness, nausea, diarrhea, and constipation (Edinoff et al, 2021). Withdrawal effects of these medications are also common and can be serious, leading to the recommendation to taper at discontinuation and to monitor patients for antidepressant discontinuation syndrome (ADS) symptoms: flu-like symptoms (lethargy, fatigue, headache, achiness, sweating), insomnia (with vivid dreams or nightmares), nausea (sometimes vomiting), imbalance (dizziness, vertigo,

light headedness), sensory disturbances ("burning," "tingling," "electric-like" or "shock-like" sensations), and hyperarousal (anxiety, irritability, agitation, aggression, mania, jerkiness) (Berber, 1998).

Other concerns with the use of SSRIs for PTSD treatment include the serious risks of overdose, increased suicidal ideation and behavior, and worsening of depression in patients treated with antidepressants. The labels of sertraline and paroxetine warn of the risk of increased suicidal ideation and behavior in children and adults aged 18 to 24 and worsening of depression in patients with major depressive disorder and other psychiatric conditions (Apotex, 2021; Pfizer, 2021).

2.3 Unmet Medical Need

PTSD is an undertreated, serious, and life-threatening condition, with 40% to 60% of patients remaining symptomatic and meeting the diagnostic criteria even after receiving treatment (Steenkamp et al, 2015; Bradley et al, 2005; Brady et al, 2000). There is a significant unmet medical need for an effective, well-tolerated treatment paradigm to adequately address treatment for patients with PTSD.

3 PRODUCT DESCRIPTION

Summary

- The proposed indication is: MDMA is an entactogen indicated for the treatment of post-traumatic disorder in combination with psychological intervention in adults
- MDMA-AT is being proposed for acute single dose use (3 split dose administrations, each separated by at least 21 days).
- The recommended use of MDMA is in conjunction with a specific therapeutic program.

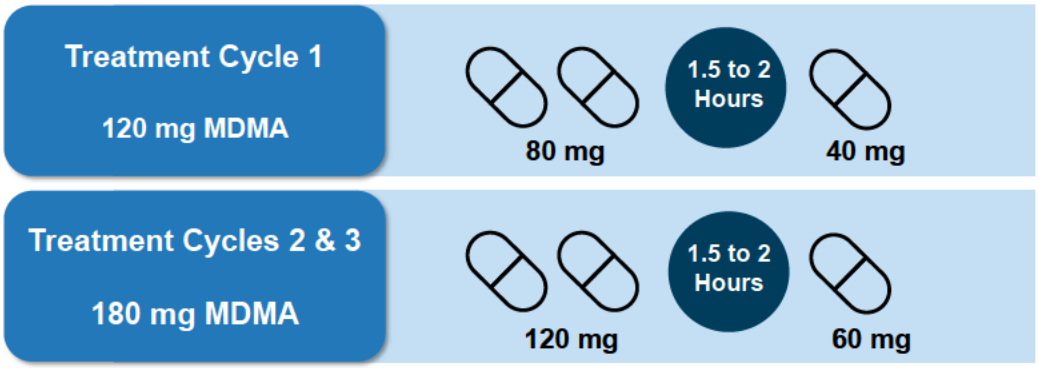
3.1 Proposed Indication

MDMA is an entactogen indicated for the treatment of post-traumatic stress disorder (PTSD) in combination with psychological intervention in adults.

3.2 Product Overview

MDMA does not require daily dosing or steady state plasma levels to be effective. It is proposed for acute single dose use (3 split dose administrations, each separated by at least 21 days) (Figure 7).

Figure 7: Treatment Administration



MDMA: 3,4-methylenedioxymethamphetamine
Note: All doses shown are for MDMA HCl (equivalent to the free base dosage strengths 102 and 150 mg MDMA that will be indicated in labeling).

The drug product is formulated as an immediate release capsule for oral administration, manufactured according to current Good Manufacturing Practices (cGMP), and is stored at room temperature. Two dosage strengths (34 and 50 mg MDMA free base; equivalent to 40 and 60 mg MDMA HCl) have been submitted for FDA review.

MDMA HCl was administered in all sponsored clinical studies and is referred to as MDMA in this document. MDMA is not currently approved for use in any market and is a new chemical entity.

3.3 Therapeutic Program

MDMA is administered in combination with psychological intervention sessions provided by a qualified healthcare provider (QHP; therapist). A psychological intervention is a non-pharmacological treatment (i.e., psychotherapy) aimed at promoting an adaptation of the individual leading to improved functionality (Horvath et al, 2011; Ricou et al, 2019). In clinical trials, the therapeutic program was conducted utilizing a specific training manual (i.e., manualized therapy).

It is intended that MDMA is used in conjunction with a specific therapeutic program consisting of preparatory psychotherapy sessions (Appendix 11.2.1), 3 medication sessions (including psychological intervention [Section 6.2.2]), and follow-up integration sessions (Appendix 11.2.2) (Figure 3).

- **Medication Session**: MDMA (3 capsules taken as a split dose separated by 1.5 to 2 hours) in combination with psychological intervention (while the patient is experiencing the acute effects of the drug). The product will be provided in single dose packaging per medication session and is available in 2 doses: 120 or 180 mg MDMA (administered as 3 capsules of the same dosage strength, 40 or 60 mg MDMA each). See Section 6.1 for details regarding dose selection.
- **Treatment Cycle:** One medication session followed by integration sessions, which are intended to allow for processing of thoughts and feelings from the

medication sessions during the weeks that follow. Medication sessions are to be separated by at least 21 days.

- **Complete Course of Treatment:** Three treatment cycles.

Table 2 summarizes the differences between the psychological intervention included in the MDMA-AT therapeutic program and other approaches to the treatment of PTSD.

Table 2: Comparison of Common Elements Therapeutic Approaches for PTSD

Therapeutic Element	MDMA-AT	CBT	EMDR	Psychodynamic Psychotherapy
Prolonged Exposure	Spontaneous recall of traumatic memories, with intermittent, non-directive discussion	In vivo / imaginal exposure	Target image combined with a non-directive approach, with intermittent discussion	Not a specific element of this approach
Cognitive Restructuring	Occurs spontaneously, with minimal therapist intervention	Explicit identification, challenging, and modification of maladaptive cognitions	Occurs spontaneously, may be catalyzed by therapist	Occurs spontaneously; may be catalyzed by therapist's interpretations
Anxiety Management and Stress Inoculation Training	Included	Included (for PTSD)	Included	Not a specific element of this approach
Increased Awareness of Positive Experiences, including Present Safety	Occurs spontaneously	May be part of cognitive restructuring or may occur spontaneously after prolonged exposure.	Occurs spontaneously	Occurs spontaneously
Clearing of Somatic Symptoms	Often occurs spontaneously with minimal therapist intervention	Therapist directs attention to the body.	Therapist directs attention to the body.	Not a specific element of this approach

CBT: Cognitive Behavioral Therapy; EMDR: Eye Movement Desensitization and Reprocessing; MDMA: 3,4-methylenedioxymethamphetamine

3.4 Mechanism of Action

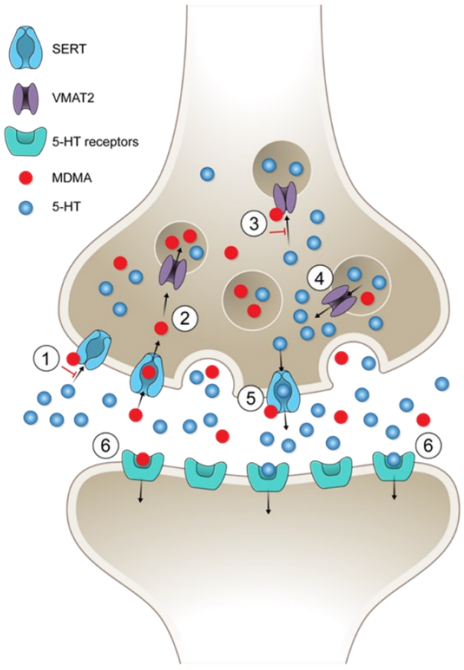
3.4.1 Molecular Mechanism of Action

MDMA is included in the pharmacological class of drugs known as “entactogens” (Nichols, 2022). This class of drug differs from hallucinogenic phenethylamines in structure and psychopharmacology. The subjective effects of this class of drug also vary from classical psychostimulant or hallucinogenic effects. As the name implies, this drug class promotes affiliative social behavior (i.e., self-compassion, empathy, and prosociality), has anxiolytic activity (i.e., promotes feelings of well-being), and may

facilitate states of introspection and personal reflection (Hysek et al, 2014; Kirkpatrick et al, 2014b). These effects are thought to be primarily mediated by release of serotonin (5-HT) (Hysek et al, 2012; Liechti et al, 2000a) and norepinephrine (Hysek et al, 2011), and the activation of 5-HT2 receptors (Liechti et al, 2000b). Additionally, MDMA releases oxytocin (Hysek et al, 2014; Dumont et al, 2009; Francis et al, 2016), which may contribute to the mediation of its prosocial effects (Ramos et al, 2013; Thompson et al, 2007). It is also known to produce mild perceptual alterations, attenuated compared with classic hallucinogens, such as lysergic acid diethylamide (LSD) and psilocybin (Holze et al, 2020).

The molecular basis for the mechanism of action of MDMA is still under study. MDMA concomitantly promotes release, inhibits reuptake, and extends duration of serotonin, and to a lesser extent, norepinephrine and dopamine in the synaptic cleft to increase monoaminergic neurotransmission (Rudnick and Wall, 1992; Verrico et al, 2007). In addition, disruption of VMAT2 function by MDMA leads to increased neurotransmitters efflux into the synapse (Lizarraga et al, 2015). Importantly, it is well established that MDMA preferentially stimulates serotonin release and results in relatively little increase in synaptic dopamine (Schenk and Highgate, 2021). For an overview of the pharmacological effects of MDMA at the serotonin terminal and synapse, see Figure 8.

Figure 8: Pharmacological Effects of MDMA at Serotonin Terminal and Synapse



- MDMA inhibits 5-HT uptake by SERT, reducing 5-HT clearance from the synapse (1).
- MDMA crosses the plasmalemmal membrane via SERT and is taken into vesicles by VMAT2 (2).
- MDMA also inhibits 5 HT uptake by VMAT2, reducing the packaging of 5-HT into vesicles (3).
- MDMA reverses transport at VMAT2, releasing sequestered 5-HT and increasing cytosolic 5-HT levels (4).
- MDMA reverses transport at SERT, increasing synaptic 5 HT levels (5).
- MDMA and 5-HT activate postsynaptic 5-HT receptors with downstream effects (6).

5-HT: 5-hydroxytryptamine (serotonin) receptor subtype; MDMA: 3,4-methylenedioxymethamphetamine; SERT: serotonin transporter; VMAT2: vesicular monoamine transporter 2
Source: Pharmacology Written Summary, Figure 1

3.4.2 Proposed Mechanism of Action Related to Therapeutic Benefit

Evidence from both clinical and nonclinical research indicate that MDMA provides the opportunity for a corrective emotional experience and cognitive processing of the trauma in the context of therapy, which may facilitate a long-term therapeutic effect. The prosocial effects of MDMA include enhanced sociability, empathy, and trust, while reducing defenses and fear of emotional injury, and making unpleasant memories less disturbing while enhancing communication and capacity for introspection (Bedi et al, 2014; Wardle and de Wit, 2014; Wardle et al, 2014; Carhart-Harris et al, 2015).

The initial therapeutic effects of MDMA-AT may be evident within a short period of treatment and may include increased feelings of interpersonal closeness, changes in social perception, and reduced anxiety. Longer term effects may be related to changes in the way a brain with PTSD processes fear memories and/or social reward learning and may lead to the long-term behavioral alterations associated with treatment effect (Nardou et al, 2019).

3.4.3 Mechanism of Action Related to Abuse Potential

Effects of MDMA are distinct from psychostimulants such as d-amphetamine and methamphetamine, which primarily activate dopamine and norepinephrine systems, with only minimal effects on serotonin (Simmler et al, 2013; Verrico et al, 2007). Typically, the higher the ratio of dopamine to serotonin released by a drug, the more likely that drug is to be abused (Schenk and Highgate, 2021). For example, SSRIs are not typically considered to be drugs of high abuse liability or likely to lead to dependence or substance use disorders (Lichtigfeld and Gillman, 1998). Thus, as MDMA is a drug that preferentially stimulates release of serotonin, it is predicted to have low abuse potential with episodic use.

However, repeated (frequent and/or extensive) MDMA use may result in compromised serotonin signaling, decreasing the inhibitory effects of serotonin, and leading to enhanced dopamine neurotransmission in response to MDMA (Schenk et al, 2011). It is this response that is thought to be responsible for the transition to disordered use and dependence. These data are further supported by nonclinical studies reporting that repeated MDMA exposure may produce a neuroadaptive response that is more aligned with other drugs of abuse (Lanteri et al, 2014).

3.5 History of MDMA

Human use of MDMA was reported as early as the late 1960s (Pentney, 2001; Shulgin and Nichols, 1978). MDMA was reported to be administered in a psychotherapeutic context in 1977 and onward, prior to MDMA being listed as a Schedule I substance in 1985 (Passie, 2018). It is estimated that MDMA was administered to thousands of people in therapeutic settings prior to scheduling and use continued around the world in various non-medical contexts after scheduling (Sumnall et al, 2006; Carlson et al, 2005; Cole and Sumnall, 2003; UNODC, 2023).

MDMA has been studied extensively in studies funded by the National Institutes of Health (NIH) and in ex-US studies. Safety and efficacy data have been reported in the published literature from over 1500 participants in non-sponsored MDMA clinical trials, and these results have supplemented the data from sponsor-conducted studies. Approximately 2000 participants have received MDMA in sponsored and non-sponsored clinical trials.

In 1985, the DEA temporarily placed MDMA under Schedule I in an emergency scheduling (DEA, 1985). Following review, the DEA administrative law judge recommended that MDMA be placed in Schedule III (DEA, 1986a). However, the DEA submitted exceptions to the recommended ruling (DEA, 1986b) and, in 1988, MDMA was classified as a Schedule I substance based on lack of accepted medical use and safety data, as well as potential for abuse, a decision that stands today (DEA, 1988).

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- MDMA was granted Breakthrough Therapy Designation by the FDA for treatment of PTSD based on Phase 2 clinical trial data.
- The Sponsor worked with the FDA on a Specialized Protocol Assessment (SPA), which resulted in agreement on the design and size of the Phase 3 clinical trials.
- FDA granted Priority Review for the MDMA NDA.

4.1 Regulatory History

In 2001, the Sponsor opened an IND application (IND 063384) to conduct an international series of Phase 1 to 3 clinical trials to investigate the medical use of MDMA-AT for treatment of PTSD. In 2017, the Sponsor worked with the FDA to reach agreement on the design and size of the Phase 3 clinical trials through a process known as a SPA. The resulting agreement was for two nearly identical Phase 3 trials to be conducted sequentially. A safety database size of 200 to 300 participants exposed to the treatment was conditionally agreed, barring any unforeseen safety signal during the first pivotal trial, based on intended limited clinical use of 3 single-dose medication sessions spaced at least 21 days apart.

Subsequently, MDMA was granted Breakthrough Therapy Designation by the FDA for treatment of PTSD based on Phase 2 clinical trial data. The Sponsor's Phase 3 program commenced in 2018, and the second of 2 nearly identical Phase 3 trials concluded in 2022 (Figure 2). Since 2016, the Sponsor met with the Agency 10 times under IND

066384 regarding the PTSD development program. In addition to these meetings, there were numerous written correspondences with the Agency.

In December 2023, the Sponsor submitted the final sequence in a series of rolling submissions and the FDA initiated filing review of the NDA for MDMA used in combination with psychological intervention for the treatment of PTSD. In February 2024, FDA filed the application and granted Priority Review.

Of note, the Sponsor has also undergone changes throughout this development program. Initially, IND 066384 was opened by MAPS in 2001. Beginning in 2015, MAPS sponsored studies were implemented through its subsidiary, MAPS Public Benefit Corporation (MAPS PBC). In 2023, MAPS transferred ownership of the IND and NDA to MAPS PBC. In 2024, MAPS PBC changed its name to Lykos Therapeutics, Inc. ("Lykos").

4.2 Development Program

4.2.1 Clinical Development

MDMA-AT has been studied in Phase 1, 2, and 3 trials. The efficacy of MDMA-AT in the treatment of PTSD has been demonstrated by the results of 2 adequate and well-controlled Phase 3 studies, supported by the results of Phase 2 studies. The safety profile is based on the results of the Sponsor's clinical development program in 17 clinical studies, with 427 participants exposed to MDMA (287 participants with PTSD and 140 healthy volunteers) and informed by the published literature. These studies are summarized below, and additional detail is provided in Table 29 (Appendix 11.1).

The primary sources of data presented in this briefing document are as follows:

- **Efficacy data**: 2 adequate and well-controlled Phase 3 clinical studies, MAPP1 and MAPP2. These pivotal, randomized, double-blind, placebo-controlled, multi-site trials were conducted in participants with PTSD.
- **Durability of the treatment response** (i.e., persistence of effectiveness following acute treatment): an observational LTFU study (MPLONG) enrolling participants from the Phase 3 studies (MAPP1 and MAPP2). All participants from parent studies MAPP1, MAPP2, MP16, MP17, and MAPPUSX were informed about the MPLONG LTFU study and given the opportunity to participate at least 6 months after their final medication session in the parent study. The durability results from participants who were enrolled in the Phase 3 studies MAPP1 and MAPP2 and subsequently enrolled in MPLONG are summarized in this briefing document.
- **Pooled safety data**: Six studies (MAPP1, MAPP2, MAPPUSX, MP-8, MP-12, MP16) were pooled for the safety analyses. Pooling rationale is provided in Appendix 11.1. The focus of the discussion of safety in this briefing document is the pooled data from the Phase 3 studies (MAPP1 and MAPP2).

- **Clinical pharmacology data**: The Sponsor conducted a healthy volunteer food effect and PK study (MPKF) and has also obtained the right to reference primary PK data from an additional 50 participants exposed to MDMA in a study conducted by National Institute on Drug Abuse (NIDA) (NCT01148342). Population PK (PopPK) and physiologically-based PK (PBPK) modeling were also conducted.

4.2.2 Nonclinical Safety and Toxicology

The Sponsor has conducted a number of nonclinical studies that included toxicokinetic assessments: single-dose and 28-day repeat-dose toxicity studies with expanded neurohistopathology (rats and dogs), fertility and early embryonic development studies (rats), and embryofetal developmental studies (rats and rabbits). Exposure of MDMA and the active metabolite, MDA, as measured by the maximum observed concentration (C_{max})and area under the curve (AUC) generally increased in a dose proportional (or greater) manner across the dose ranges evaluated in nonclinical studies, with no notable differences in exposure related to sex and no evidence of accumulation or reduction in exposure after repeat administration.

In vitro and in vivo safety studies addressing genotoxicity, fertility, early embryonic development, and embryofetal development suggest no liability of MDMA. Overall, MDMA was well-tolerated with no mortality or significant toxicologic findings after oral administration in rats at doses ≤ 20 mg/kg and in dogs at doses ≤ 4 mg/kg. These no observed adverse effect level (NOAEL) doses resulted in 6.5 times (female rat), 4.5 times (male rat), and 0.9 times (female and male dog) the human exposure based on C_{max} of 120 mg MDMA dose. The safety margins determined in the nonclinical toxicology studies relative to the anticipated human exposures suggest a narrower therapeutic margin in the dog, where unexplained deaths were observed at higher doses. However, those findings are mitigated by clinical studies of MDMA, in which it has been generally well-tolerated.

The nonclinical data overall established a general lack of liability of MDMA regarding genotoxicity, embryo-fetal effects, and prolongation of the QT interval (interval from Q wave to the end of T wave) and established the acceptable tolerability profile of MDMA at the study NOAELs.

5 CLINICAL PHARMACOLOGY

Summary

- Metabolites of MDMA include the minor but active metabolite MDA and the major inactive metabolite HHMA.
- MDMA is not a substrate for intestinal or hepatic transporters and is not actively transported into tissues.

- MDMA is primarily eliminated by hepatic metabolism with minimal renal contribution.
- MDMA is a strong CYP2D6 inhibitor and has been shown to perpetrate PK drug interactions due to inhibition of CYP2D6.
- MDMA is also metabolized by CYP2D6, but no meaningful interactions have been described with MDMA as a victim of DDI.
- PopPK analyses did not identify any clinically significant covariates by age, sex, race, or food consumption.
- A food effect study demonstrated that the pharmacokinetics of MDMA are bioequivalent when MDMA is administered with or without food. Absorption was delayed when administered with food.
- Onset of MDMA effects occurs 30 to 60 minutes after oral administration, peak effects occur 75 to 120 minutes post-drug, and the duration of effects lasts from 3 to 6 hours.

5.1 Clinical Pharmacology Clinical Studies

The assessment of clinical pharmacology is based on data from the published literature as well as the following clinical studies:

MPKF study: This sponsored-study was a Phase 1, single center, open-label, randomized sequence, 2-period cross-over study to determine the effect of food on the relative bioavailability of MDMA in healthy volunteers. The study included 16 healthy participants who were administered single doses of 120 mg MDMA under fed and fasted conditions, with a washout period of 14 days. PK sampling, vital signs monitoring, and electrocardiogram (ECGs) were collected up to 72 hours after dosing.

NIDA study (right of reference obtained by Sponsor): This study, sponsored by NIDA, was a Phase 1 placebo-controlled, double-blind, 3-period crossover study conducted in 50 healthy volunteers. Participants were administered a single dose of placebo, a low dose (1.0 mg/kg) of MDMA, and a high dose (1.6 mg/kg) of MDMA (Hartman et al, 2014; Schwaninger et al, 2011; Abraham et al, 2009; Kolbrich et al, 2008a). A washout period of a minimum of 7 days was implemented prior to each subsequent treatment. Participants enrolled in the NIDA study had a recent prior history of drug use including prior MDMA use. The Sponsor obtained right to reference PK and assay validation data from this study.

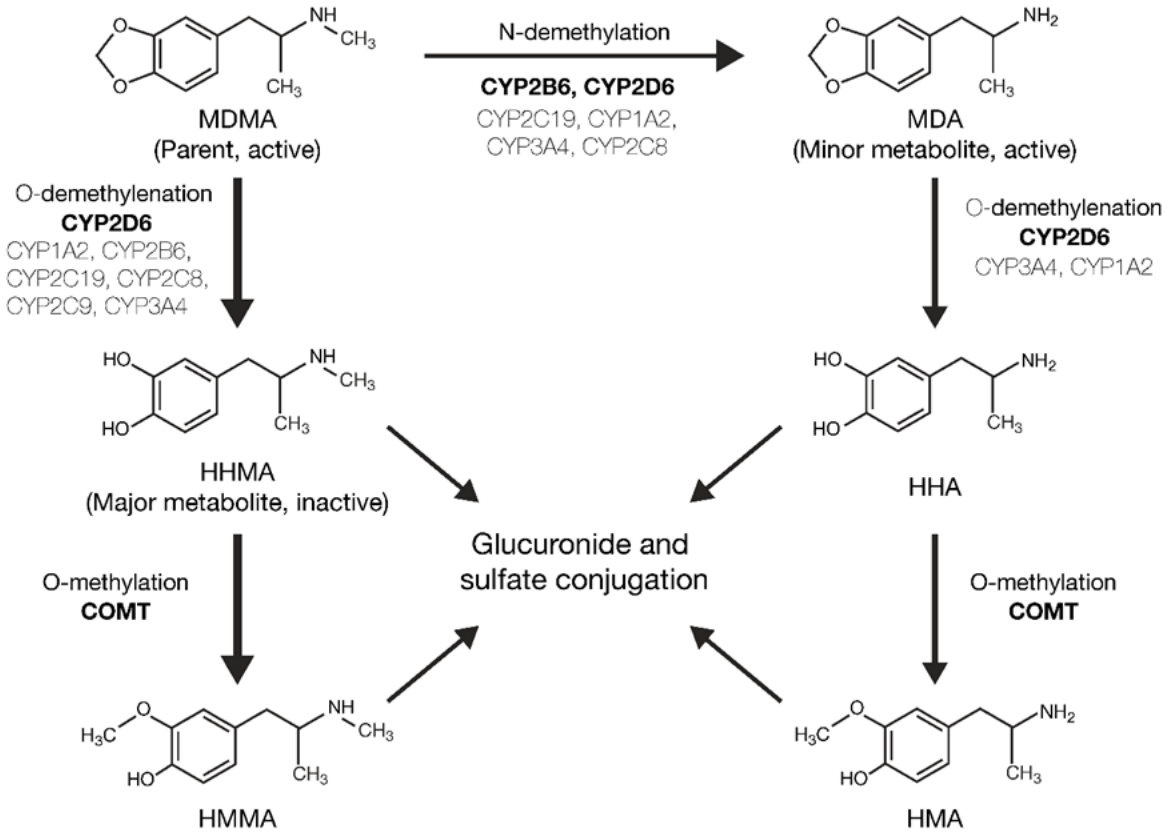
Data from the MPKF and NIDA studies were utilized in PopPK analyses and PBPK modeling.

5.2 Metabolism

MDMA is metabolized via hepatic N-demethylation to form the minor and active metabolite MDA and is demethylenated to form the major inactive metabolite HHMA

(Figure 9). MDA is formed primarily by CYP2B6, and to a lesser extent by CYP2D6, with minor contributions from additional cytochrome P450 (CYP) isozymes (CYPs 2C19, 1A2, 3A4, and 2C8). HHMA is formed primarily by CYP2D6, with minor contribution from additional CYP450 isozymes (CYPs 1A2, 2B6, 2C19, 2C8, 2C9, and 3A4). The fraction metabolized via CYP2D6 is estimated to be 0.85 per the Sponsor's PBPK model. Metabolites are primarily excreted as glucuronide and sulfate conjugates (Steuer et al, 2015a; Steuer et al, 2015b; Schwaninger et al, 2011; Abraham et al, 2009; Helmlin et al, 1996).

Figure 9: Metabolism of MDMA in Humans



COMT: catecholamine-O-methyltransferase; CYP: cytochrome P450; HHA: 3,4-dihydroxyamphetamine; HHMA: 3,4-dihydroxymethamphetamine; HMA: 4-hydroxy-3-methoxyamphetamine; HMMA: 4-hydroxy-3-methoxymethamphetamine; MDA: 3,4-methylenedioxyamphetamine; MDMA: 3,4-methylenedioxymethamphetamine
Source: Summary of Clinical Pharmacology Studies, Figure 5

5.3 Pharmacokinetics

Highlights of MDMA PK include:

- MDMA is readily absorbed following oral administration, with time of observed maximum concentration (T_{max}) of 2 hours under fasting conditions and 4 hours when MDMA is administered with a high-fat/high-calorie meal (MPKF study).

- MDMA has been shown to be partially bound to plasma proteins in humans. The mean unbound fraction of MDMA in human plasma was 83.5%.
- MDMA's large volume of distribution is consistent with the relatively low plasma protein binding.
- The oral clearance (CL/F) of MDMA was 29.5 L/hr (MPKF study).
- Half-life ($t_{1/2}$) was 8.7 hours following a single dose of 120 mg MDMA (MPKF Study).
- MDMA is not a substrate for intestinal transporters (MDR1, BSEP, and BCRP) or hepatic transporters (OATP1B1 and OATP1B3) and is not actively transported into tissues.
- Renal excretion of MDMA and metabolites is low (<20%) (Abraham et al, 2009; Schwaninger et al, 2011). MDMA is not likely to exhibit altered PK in patients with renal impairment. A renal impairment study was therefore not required by the FDA.

MDMA has a large degree of interindividual variability in PK, likely due to MDMA inhibition of CYP2D6 and thus its own metabolism. CYP2D6 genotype has a small impact on MDMA PK that is not clinically meaningful (MPKF study; Schmid et al, 2016). PopPK analyses did not identify any clinically significant covariates by age, sex, race, or food consumption.

Study MPKF demonstrated no effect of food on the C_{max} and AUC of MDMA or MDA. There was a delay in the T_{max} when MDMA was administered in the fed state with a high-fat/high-calorie meal, which did not generally affect the time course of subjective effects. Thus, MDMA can be administered with or without food.

In the proposed treatment of PTSD, MDMA is to be administered as a split dose to extend peak effects. In the PBPK model, the overall C_{max} and AUC did not differ meaningfully between simulated single doses and split doses for the same total dose. However, split dose administration of MDMA reduced AUC within the first 4 hours and T_{max} was delayed by approximately 1 hour, relative to single dose administration, consistent with the intent to facilitate a more gradual onset and extend peak effects.

The PK of MDMA has not been studied in patients with hepatic impairment. Hepatic metabolism of MDMA is a major route of its elimination (de la Torre et al, 2000; de la Torre et al, 2004). A post-marketing PK study is planned in participants with moderate hepatic impairment.

5.4 Drug-Drug Interactions (DDIs)

5.4.1 Effect of MDMA on Other Drugs

MDMA has been shown to be a rapid, potent, reversible, and time-dependent CYP2D6 inhibitor (Kolbrich et al, 2008a; de la Torre et al, 2004; Sponsor's in vitro data). No

clinical studies have been conducted by the Sponsor evaluating clinical PD- or PK-related DDIs of MDMA. The Sponsor's in vitro data, PBPK modeling, and a review of literature describing clinical DDIs with MDMA indicates that the primary liability of MDMA is as a perpetrator of DDI when administered in combination with sensitive CYP2D6 substrates. These changes may be clinically meaningful. The PBPK model substantiated these effects.

- *Effect of MDMA on CYP2D6 substrates*: Published and clinical DDI studies have demonstrated ~10-fold higher plasma levels of dextromethorphan when administered with MDMA (O'Mathúna et al, 2008; Yubero-Lahoz et al, 2011). Paroxetine is a serotonin reuptake inhibitor that is sometimes prescribed for individuals with PTSD and is metabolized in part via CYP2D6. MDMA was demonstrated to increase the C_{max} and AUC_{0-8} of paroxetine by 2.5- and 3-fold, respectively (Segura et al, 2005).
- MDMA was identified to be an in vitro weak inhibitor of renal transporters at high concentrations in sponsored in vitro studies. However, PBPK modeling of the effects of MDMA on metformin, a drug sensitive to renal transport, identified no clinically meaningful DDI.

MDMA and paroxetine are both strong CYP2D6 inhibitors. Paroxetine is inherently ~100-fold more potent as a CYP2D6 inhibitor than MDMA (K_i 0.15 uM and 26.2 uM, respectively) (Crewe et al, 1992). However, they differ in the clinical plasma concentrations and dosing regimens required for efficacy. MDMA is designed for single-dose use repeated three times at least 21 days apart, whereas paroxetine is a daily chronic medication. The effect of MDMA on the sensitive CYP2D6 substrate, dextromethorphan (~10-fold increase in dextromethorphan plasma concentrations) is similar to the effect of paroxetine on the CYP2D6 substrate desipramine (~6-fold increase in desipramine plasma concentrations) (Alderman et al, 1997).

DDIs in the Proposed Labeling:

- Prescribers should consider dose adjustment for drugs metabolized by CYP2D6, particularly for those with a narrow therapeutic index, or use an alternative medication.
- Clinical DDI data (in vitro, simulated, and published) indicate that MDMA is a strong CYP2D6 inhibitor and should be administered with caution with CYP2D6 substrates, particularly those with a narrow therapeutic index.
- Concomitant use of MDMA and monoamine oxidase inhibitor (MAOIs) within 14 days is contraindicated because of an increased theoretical risk of causing hypertensive reactions and serotonin syndrome. At least 14 days should elapse between discontinuation of an MAOI and treatment with MDMA. As with other drugs with this mechanism of action (MOA), there is a theoretical risk of developing serotonin syndrome when MDMA and SSRIs are concomitantly administered.

5.4.2 Effect of Other Drugs on MDMA

The effect of the CYP2D6 inhibitors paroxetine and bupropion on the PK of MDMA has been evaluated in clinical studies (Segura et al, 2005; Schmid et al, 2015). These studies demonstrated no clinically meaningful effect of CYP2D6 inhibitors on the PK of MDMA. This is likely because MDMA inhibits its own CYP2D6-mediated metabolism and thus additional CYP2D6 inhibition is not impactful. These data were substantiated by the PBPK model.

5.5 Pharmacodynamics

In humans, the onset of MDMA effects occurs 30 to 60 minutes after oral administration (Cami et al, 2000; Mas et al, 1999), peak effects appear 75 to 120 minutes post-drug (Kolbrich et al, 2008a; Tancer and Johanson 2003; Harris et al, 2002; Liechti et al, 2001; Vollenweider et al, 1998), and the duration of effects lasts from 3 to 6 hours (Harris et al, 2002; Liechti et al, 2001; Vollenweider et al, 1998). In the Phase 3 studies MDMA was administered as a split dose (80 mg followed by 40 mg and 120 mg followed by 60 mg).

Most effects of MDMA likely arise directly from monoamine reuptake inhibition and release at the monoamine transporters, and indirectly from activation of downstream monoamine receptors and subsequent secretion of neuromodulators oxytocin and arginine vasopressin (AVP). MDMA binds primarily to membrane-bound monoamine transporters, which remove monoaminergic neurotransmitters from the synaptic cleft (Figure 8).

MDMA has a diverse array of secondary pharmacodynamics. MDMA has effects outside the CNS; namely on the cardiovascular, osmoregulatory, thermoregulatory, and immune systems. MDMA causes increases in blood pressure (BP) and heart rate (HR) in small mammals, primates, and humans. These effects are possibly controlled through increased sympathomimetic activity via beta adrenergic receptors (Schindler et al, 2014; Tiangco et al, 2005; Cole and Sumnall, 2003).

The neuropharmacological effects of MDMA persist well beyond the clearance of MDMA from the body (Greer and Tolbert, 1986), presumably due to effects of MDMA on brain plasticity and openness to experience (Sottile and Vida, 2022). This contrasts with the physiological effects of MDMA, which occur more temporally associated with plasma levels of MDMA (Farré et al, 2015; Peiro et al, 2013).

6 CLINICAL EFFICACY

Summary

- The adequate and well-controlled Phase 3 studies demonstrated statistically significant and clinically meaningful differences between the MDMA-AT group and the placebo with therapy group in the primary and key secondary endpoints, and, therefore, met the evidentiary standard for demonstration of efficacy.
- Treatment benefit was demonstrated in overall improvement in PTSD symptom severity, as assessed by an accepted endpoint for demonstration of efficacy in this indication, the CAPS-5 TSS. A numerical difference in both the CAPS-5 TSS with MDMA-AT compared to placebo was seen by Week 7 and increased at subsequent timepoints.
- There was also a greater proportion of participants in the MDMA-AT group than in the placebo group who met the CAPS-5 definitions of Responder, Loss of PTSD Diagnosis and In Remission, demonstrating the clinical relevance of the treatment benefit.
- Improvement in functional impairment was assessed by the key secondary endpoint, SDS and also demonstrated a statistically significant difference from placebo, which further supports the treatment benefit.
- Supportive evidence of long-term efficacy for MDMA-AT comes from the LTFU non interventional study MPLONG which evaluated evidence of durability of the treatment effect after acute treatment with MDMA-AT at ≥ 6 months following the last medication session in the parent study.

6.1 Dose Selection and Justification

The proposed dosing regimen is 3 medication sessions in combination with psychological intervention separated by at least 21 days. The second part of the split dose is administered 1.5-2 hours after the initial dose:

- Medication Session 1: 120 mg MDMA (Split: 80 mg + 40 mg)
- Medication Sessions 2 and 3: 180 mg MDMA each (Split:120 mg + 60 mg)

The rationale for the proposed dosing regimen is as follows:

Split Dosing: A split dose modality may facilitate a more gradual onset and subsidence of the effects of MDMA and may extend the peak effects of MDMA and the medicated therapy session by 2 hours (from 4 to 6 hours) without producing physiological effects that meaningfully exceed the effects occurring after the initial dose (Peiro et al, 2013; Greer and Tolbert, 1998; Greer and Tolbert, 1998).

Dose Interval: The time interval between medication sessions (approximately 3 to 5 weeks) was designed to allow sufficient time for non-drug integration sessions to occur and for participants to process and integrate the outcomes of the prior medication session.

Increased Dose After First Session: To allow patients to get acclimated to the treatment regimen and setting, a lower dose of MDMA was selected for the first medication session. Although the default option was to escalate the dose at medication sessions 2 and 3, participants could remain at the dose level of medication session 1.

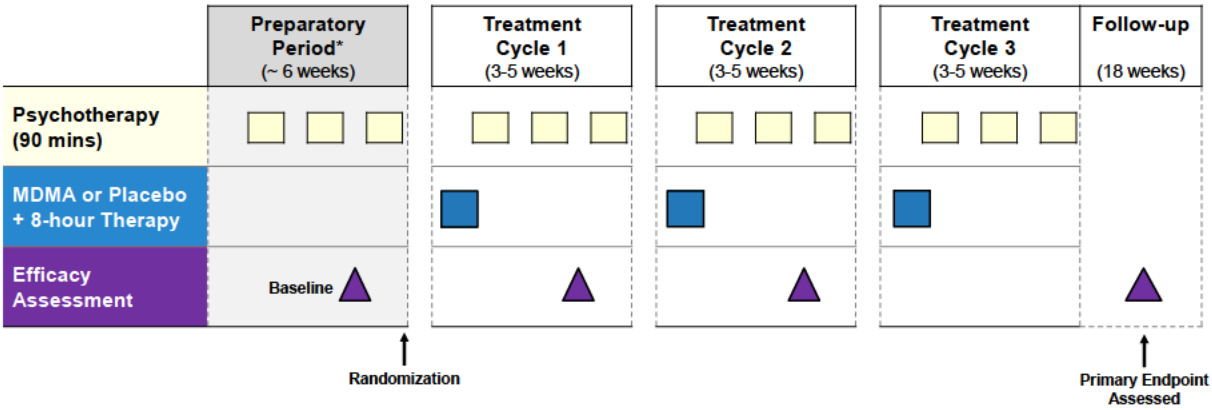
Number of Sessions: The rationale for the 3 medication sessions studied in Phase 3 was based on evaluations conducted on Phase 2 data. A review of Phase 2 efficacy data is presented in Appendix 11.4:

- A greater treatment effect was observed in active dose participants receiving 3 medication sessions (n = 51) compared to 2 medication sessions (n = 72).
- No further effect was observed when comparing participants who received 4-6 medication sessions (n = 6) in 2 Phase 2 studies compared to those who received 3 medication sessions.

6.2 Pivotal Study Design (MAPP1 and MAPP2)

The two Phase 3 pivotal trials, MAPP1 and MAPP2, were confirmatory, randomized, double-blind, placebo-controlled, multi-site studies conducted sequentially to evaluate safety and efficacy in participants with severe PTSD (MAPP1) and at least moderate PTSD (MAPP2) which utilized the same design. Figure 10 summarizes the design of the MAPP1 and MAPP2 studies.

Figure 10: MAPP1 and MAPP2 Clinical Design



*1:1 randomization and baseline endpoint evaluations were conducted following first independent rater (IR) video assessment.

Screening and Preparation: In both pivotal studies, potential participants were screened for eligibility and underwent three 90-minute preparatory psychotherapy

sessions (over approximately 6 weeks; Appendix 11.2.1) to receive further psychoeducation about PTSD, establish rapport with the therapists (i.e., develop the therapeutic alliance), and prepare for the first medication session. During this preparatory period participants discontinued prohibited medications that could confound the efficacy results. Prohibited medications included any used for the treatment of PTSD (e.g., SSRIs, SNRIs, cannabis) and any medication with significant serotonergic effect (e.g., St. John's Wort).

Following completion of 2 preparatory sessions and a washout period for patients taking any prohibited psychiatric medication, the Independent Rater (IR) confirmed PTSD severity via the CAPS-5. Patients who met final eligibility criteria were randomized 1:1 to receive either MDMA-AT or placebo with therapy and underwent a final preparatory psychotherapy session. Randomization was stratified by site and performed via an Interactive Web-based Randomization System (IWRS).

Treatment: Three treatment cycles were planned, each lasting 3 to 5 weeks and including an 8-hour medication session and 3 weekly 90-minute integration sessions. Patients took 120 mg split dose at the medication session in treatment cycle 1 and 180 mg split dose at the medication sessions in treatment cycles 2 and 3 (Table 3). The total duration of the treatment course was approximately 12 weeks.

Efficacy assessments were conducted by blinded, centralized IRs who met with the patient over live video conference between the second and third integration visits in treatment cycles 1 and 2, and approximately 6-8 weeks after completion of the third treatment cycle (i.e., primary efficacy outcome was assessed approximately 18 weeks post-Baseline) (Figure 10).

Table 3: Dose Regimen of MDMA-AT or Placebo in Studies MAPP1 and MAPP2

Medication Session	Split Dose Administration (MDMA HCl)		Total Dose (mg)
	First part (mg)	Second part (mg)	
1	80	40	120
2 and 3	120	60	180

MDMA: 3,4-methylenedioxymethamphetamine
Source: MAPP1 CSR Amendment, Table 3; MAPP2 CSR, Table 3

6.2.1 Choice of Control

Placebo with identical psychotherapy (as was provided to the MDMA group) was chosen as the comparator for Phase 3 with Agency consultation. To address functional unblinding, other controls (e.g., active placebo [low dose of MDMA with therapy] or niacin) were considered, discussed with the FDA, and ruled out for their inability to adequately address functional unblinding and/or due to a potential anti-therapeutic effect with the potential to advantage the active treatment arm.

6.2.2 Psychological Intervention

The underlying therapeutic program was administered to both treatment arms. This therapy was conducted utilizing a specific training manual and sessions were rated for adherence and were required to last 8 hours to establish a standardized approach to treatment.

The MDMA-Assisted Psychotherapy Treatment Manual was informed by previous therapeutic use of MDMA and developed for use in the MDMA development program (Mithoefer et al, 2017; Greer and Tolbert, 1998; Metzner and Adamson, 2001). The therapeutic approach:

- Was largely non-directive; inviting inquiry and providing suggestion rather than directing the patient.
- Relied on active or engaged listening and responding and support for approaching difficult material.
- Included periods of introspection alternating with periods of communication between therapists and the patient.
- Required cultural sensitivity in support of effective, sensitive communication with patients from different cultures.

The Sponsor plans to provide the training used in the clinical trials to therapists in the post-marketing setting (Section 8).

6.2.3 Study Blinding and Bias Minimization

CNS-active drugs with rapid onset of psychoactive effects are often functionally unblinding and thus, present a challenge in the design of double-blind studies (FDA, 2023). The following methods were implemented in agreement with FDA to minimize the impact of functional unblinding on the efficacy results.

Blinded, Centralized Independent Raters: Efficacy assessments were conducted by a pool of mental health professionals with graduate-level training in psychology, social work, or counseling and at least 1 year of experience working with a trauma-exposed population. These assessors also received expert training in the administration of the primary and key secondary outcome measures. Efficacy assessments were conducted in accordance with the administration guidelines in a neutral and non-leading manner. Continuous training and inter-rater reliability review were implemented to ensure quality of the endpoint data.

IRs were blinded to study design, assessment timepoint (except baseline), and safety data collected by sites, and no IR was to assess the same patient more than once. IRs were not onsite and conducted assessments over live video conference. Study participant interviews were structured to avoid discussion of participants' experience during the treatment period and were reviewed for fidelity and central reliability.

IR Database: A separate electronic data capture (EDC) database was implemented for data collected by the blinded IR Pool. This EDC had limited/controlled access and was only accessible by the IR Coordinators, the IR Monitor, and the Lead Senior IR who was responsible for the quality of the endpoint data. No other Sponsor or site staff engaged in study conduct had any access to this data.

Therapist-Investigators and Consistent Therapeutic Methodology: Therapist-investigators were required to complete extensive, multi-week training on the treatment manual. Therapist-investigators were not involved in any efficacy assessments. During the trials, ongoing training and assessment was conducted by adherence raters and clinical supervisors to ensure consistent therapeutic methodology was applied for preparatory psychotherapy, medication sessions, and integration visits. In Phase 3, adherence reviews were conducted using a 20-item checklist (e.g., “If the patient repeatedly avoided trauma-related material, the therapists gently encouraged collaborative exploration”).

Unblinded Independent Data Monitoring Committee (iDMC): Acted in an advisory capacity to oversee patient safety and with the responsibility of conducting an administrative interim analysis for sample size re-estimation when enrollment was complete and 60% of primary endpoint data had been obtained in the pivotal trials. No changes to the sample sizes in either study were made as a result of these interim analyses.

6.2.4 Enrollment Criteria

The inclusion and exclusion criteria were generally similar between the 2 Phase 3 studies and included the following:

- **General inclusion/exclusion criteria**: implemented to ensure participants were adults weighing more than 48 kg, who were willing and able to participate in the study including agreeing to specific lifestyle modifications. Participants were excluded if they were likely to be re-exposed to their index trauma or other significant trauma, they lacked social support, or lacked a stable living situation.
- **Underlying disease status (inclusion criteria):** At Screening, participants in both studies were required to meet DSM-5 criteria for current PTSD with a symptom duration of 6 months or longer. Symptom severity on the PTSD checklist for DSM-5 (PCL-5) and CAPS-5 was used to determine the severity of PTSD at screening (PCL-5) and baseline (CAPS-5) and participants were required to have at least severe (MAPP1) or moderate (MAPP2) PTSD.
    - At screening, PCL-5 total score of ≥46 (MAPP1) or ≥40 (MAPP2)
    - At baseline, CAPS-5 total severity score of ≥35 (MAPP1) or ≥28 (MAPP2)
- **Current suicide risk**: History of suicide attempts and non-suicidal self-injurious behavior were not exclusionary. However, at baseline any serious suicide risk, likelihood to require hospitalization related to suicidal ideation and behavior, any

suicidal behavior including suicide attempts or preparatory acts (within the last 6 months of the assessment) or Suicidal ideation scores of ≥4 (within the last month of the assessment at a frequency of once a week or more) or 5 (within the last 6 months of the assessment) on the Baseline C-SSRS was exclusionary.

- **Prior drug use**: Limited prior use of illicit MDMA was allowed. However, use >10 times within the 10 years prior to enrollment or at least once within 6 months of the first Medication Session was exclusionary. Ketamine-assisted therapy or ketamine use within 12 weeks of enrollment was also exclusionary.
- **Allowable comorbidities**:
    - **Well-controlled hypertension** successfully treated with antihypertensive medicines (required to conduct additional screening to rule out underlying cardiovascular disease). Uncontrolled essential hypertension was exclusionary.
    - **Asymptomatic Hepatitis C (HCV)** (previously undergone evaluation and treatment as needed)
    - **Alcohol or cannabis use disorder** (mild or moderate in early remission for 3 months prior to enrollment). Severe or moderate not in early remission alcohol or cannabis use disorder were exclusionary.
    - **Type 2 diabetes mellitus** (history of, or current; required to conduct additional screening to rule out underlying cardiovascular disease and to assess whether the condition was stable and effectively managed)
    - **Hypothyroidism** (if taking adequate and stable thyroid replacement medication)
    - **Glaucoma** (history of, or current; required approval from an ophthalmologist)
- **Other excluded psychiatric conditions**
    - **Electroconvulsive therapy** (within 12 weeks of enrollment)
    - **Primary psychotic disorder, Bipolar disorder 1, or Dissociative identity disorder** (history of, or current)
    - **Eating disorder with active purging** (current)
    - **Major depressive disorder with psychotic features**
    - **Active illicit (other than cannabis) or prescription drug substance use disorder (**any severity within 12 months prior to enrollment)
    - **Personality Disorders** Cluster A (paranoid, schizoid, schizotypal), B (antisocial, borderline, histrionic, narcissistic), or C (avoidant, dependent, obsessive-compulsive)

- **Required ongoing concomitant therapy with a psychiatric medication** (with exceptions).

- **Other excluded cardiovascular (CV)-related history**
  - **Significant cardiovascular or cerebrovascular disease** evaluated by cardiac stress test and carotid artery ultrasound, if moderate cardiovascular risk assessed at screening (e.g. well controlled hypertension, type 2 diabetes, etc.)
  - **History of myocardial infarction, cerebrovascular accident, or aneurysm** (or other medical conditions that could make receiving a sympathomimetic drug harmful because of increases in BP and heart rate).
  - **History of arrhythmia** within 12 months of screening, other than occasional premature ventricular contraction (PVCs) in the absence of ischemic heart disease; Wolff-Parkinson-White syndrome (or any other accessory pathway not successfully eliminated by ablation); marked prolongation of QT/QTc interval, history of additional risk factors for Torsade de pointes, require use of QT/QTc interval prolonging medications

- **Other excluded medical history**
  - **Symptomatic liver disease** or have significant liver enzyme elevations
  - **History of hyponatremia or hyperthermia**

6.3 Pivotal Phase 3 Study Endpoints

The following efficacy endpoints were included in both pivotal Phase 3 studies (MAPP1 and MAPP2):

- **Primary**: LS mean change in CAPS-5 TSS from Baseline to Week 18.
- **Key secondary**: LS mean change in clinician-rated functional impairment, as measured by the SDS from Baseline to Week 18.
- **Exploratory**: LS mean change in exploratory measures from Baseline to Week 18.

The primary (Section 6.3.1) and key secondary (Section 6.3.2) efficacy measures utilized in the pivotal Phase 3 studies are standard measurements, widely used in clinical trials and generally recognized as reliable, accurate, and relevant for the assessment of participants with PTSD, as described below.

6.3.1 Primary Efficacy Measure: CAPS-5

The CAPS-5 is a clinician-administered structured diagnostic interview used to assess DSM-5 PTSD diagnostic status and symptom severity developed by the National Center

for PTSD (Weathers et al, 2013). It has been extensively validated, is considered the gold standard in PTSD severity assessment by health professionals, is widely used as the primary outcome measure in PTSD clinical trials and accepted by regulatory agencies.

Individual Item Scores: The first 20-items on the CAPS-5 correspond to the 20 DSM-5 PTSD symptoms:

Intrusive memories, nightmares, flashbacks, emotional and physical reactions, avoidance of thoughts and feelings, avoidance of external reminders, psychogenic amnesia, negative beliefs, distorted self-blame, persistent negative affect, decreased participation in activities, interpersonal estrangement, inability to experience positive affect, anger outbursts, risky or self-destructive behavior, hypervigilance, exaggerated startle reactions, concentration problems, and sleep disturbance.

In order to rate each item, the rater asks a series of standardized prompts for each item, combines information obtained about the frequency and intensity of each symptom, and makes a single severity rating for each item, which ranges from 0 to 4 (Table 4).

Table 4: Symptom Severity Rating Scale

Score	Rating	Description
0	Absent	The respondent denied the problem or the respondent's report does not fit the DSM-5 symptom criterion.
1	Mild/ subthreshold	The respondent described a problem that is consistent with the symptom criterion but is not severe enough to be considered clinically significant. The problem does not satisfy the DSM-5 symptom criterion, and thus does not count toward a PTSD diagnosis.
2	Moderate/ threshold	The respondent described a clinically significant problem. The problem satisfies the DSM-5 symptom criterion and thus counts toward a PTSD diagnosis. The problem would be a target for intervention. This rating requires a minimum frequency of "2× month" or "some of the time (20-30%)" plus a minimum intensity of "Clearly Present".
3	Severe/ markedly elevated	The respondent described a problem that is well above threshold. The problem is difficult to manage and at times overwhelming and would be a prominent target for intervention. This rating requires a minimum frequency of "2× week" or "much of the time (50-60%)" plus a minimum intensity of "Pronounced".
4	Extreme/ incapacitating	The respondent described a dramatic symptom, far above threshold. The problem is pervasive, unmanageable, and overwhelming, and would be a high-priority target for intervention.

Source: CAPS-5 Version dated 01 May 2015 (version used in MAPP1, MAPP2, and MPLONG).

CAPS-5 TSS: calculated by summing each of the 0 to 4 severity scores from items 1 through 20, for a total possible score of 80, with higher scores reflecting higher PTSD severity. CAPS-5 TSS are categorized into 5 groups based on symptom severity (asymptomatic to extreme). A 10-point reduction in CAPS-5 TSS is considered to be clinically meaningful for a participant and an acceptable assessment for demonstration of treatment benefit in PTSD (Schnurr et al, 2022; Varker et al, 2020). A 10-point reduction in CAPS-5 TTS can be clinically experienced by patients as dramatic change

in several symptoms or moderate changes across many symptoms and is typically accompanied by notable improvement in social and occupational impairment. Responder definitions based on CAPS-5 are presented in Table 5.

Table 5: CAPS-5 Responder Analysis Classifications

Classification	Definition
Responder	≥ 10-point reduction in CAPS-5 TSS
Loss of Diagnosis	≥ 10-point reduction in CAPS-5 TSS AND does not meet diagnostic criteria
Remission	CAPS-5 TSS ≤ 11 (asymptomatic) AND does not meet diagnostic criteria

CAPS-5: Clinician Administered PTSD Scale for DSM-5, TSS: Total Severity Score

6.3.2 Key Secondary Efficacy Measure: SDS

The SDS is a validated, patient-rated 3-item assessment of functional impairment associated with PTSD. It measures the severity of disability (i.e., the degree of impairment) in the domains of work, family life/home responsibilities, and social/leisure activities. Responses are recorded using an 11-point scale (0 = not at all to 10 = extremely) and 5 verbal tags (not at all [score=0], mildly [score=1-3], moderately [score= 4-6], markedly [score=7-9], extremely [score=10]). The SDS has high internal consistency and accurately identified 80% of a sample of primary care participants with mental disorders (Leon et al, 1997). In the Phase 3 studies, the SDS was administered by the IRs who also administered the CAPS-5.

The SDS was modified per FDA's request to limit the impact of missing item-level data.

- Functional impairment in the domain of work was imputed as a 10 for participants who were not able to work for reasons related to PTSD.
- The impact of missing item-level data was further mitigated by using an average score (maximum score: 10), rather than a summed score (maximum score: 30).
- Functional impairment in the domain of work was skipped for participants who were not able to work for reasons unrelated to PTSD and this reason was collected.

The definitions of responder, remission, and non-responder are summarized in Table 6 (Sheehan 2008).

Table 6: Definitions for Responder Analysis on the Key Secondary Endpoint

Outcome	Definition
Responder	Participants with a 4-point or greater reduction in average SDS total score
Remission of Functional impairment	Responders with an average SDS total score of less than 3
Non-Responder	Participants with less than a 4-point reduction in average SDS total score

SDS: Sheehan Disability Scale
Source: Appendix 16.1.1; Section 14.2.1.3.

6.3.3 Exploratory Efficacy Measures

Exploratory efficacy measures performed in the MAPP1 and MAPP2 studies are presented in Table 7.

Table 7: Description of Exploratory Measures

Measure	Description	Score Interpretation
AUDIT	Self-reported measure to detect alcohol abuse disorders	Higher numbers indicate more problematic alcohol use
BDI-II	Self-reported measure to assess depression symptom severity	Higher scores indicate greater severity of depressive symptoms
CAPS-5 subscales	CAPS-5 subscales B, C, D, E, and G scores (severity only)	Higher scores indicate greater severity in PTSD symptoms
CPGS	Self-reported measure to assess pain	Higher numbers on a Likert scale indicate higher severity of pain and/or disability
DSP-I	Clinician-administered measure to detect and assess severity of the dissociative type of PTSD	Higher scores indicate more severe dissociative symptoms
DUDIT	Self-reported measure designed to assess presence of substance use disorders	Higher numbers indicate more problematic use of substances
EAT-26	Self-reported measure to assess presence of eating disorders	Higher numbers on a Likert scale indicate higher risk of disordered eating
EQ-5D-5L	Self-reported questionnaire to assess health status	Higher index scores indicate a higher overall health status
HPQSF	Self-reported measure to assess absenteeism and work performance	Higher scores on a Likert scale indicate higher quality performance in the workplace
IASC	Self-reported measure to assess difficulties with relationships, identity, and affect regulation	Higher scores on a Likert scale indicate higher frequency of events or experiences associated with the difficulties with relationships and identity
IPF	Self-reported measure to assess psychosocial functioning	Higher scores on a Likert scale indicate greater impairment
LEC-5	Evaluates exposure to traumatic events	None
SCS	Self-reported measure to assess self-compassion	Higher scores on a Likert scale indicate higher levels of self-compassion
SRNU	A sponsor-developed measure to assess participant's use of nicotine	None; evaluates the frequency of nicotine use

Measure	Description	Score Interpretation
TAS-20	Self-report measure to assess difficulty recognizing and verbalizing emotions	Higher numbers on a Likert scale indicate greater difficulty recognizing and verbalizing emotions
UFEC	Self-reported, sponsor-developed measure to assess participant healthcare utilization	Higher scores indicate greater use of healthcare facilities

AUDIT: Alcohol Use Disorders Identification Test; BDI-II: Beck Depression Inventory II; CAPS-5: Clinician-administered PTSD Scale for DSM-5; CPGS: Chronic Pain Grade Scale; DSP-I: Dissociative Subtype of PTSD Interview; DUDIT: Drug Use Disorders Identification Test; EAT-26: Eating Attitudes Test; EQ-5D-5L: EuroQol Five Dimensions – Five Levels Questionnaire; HPQSF: Health and Work Performance Absenteeism and Presenteeism Short Form; IASC: Inventory of Altered Self Capacities; IPF: Inventory of Psychosocial Functioning; LEC-5: Life Events Checklist for DSM-5; PTSD: post-traumatic stress disorder; TAS-20: Toronto Alexithymia Scale; SCS: Self-Compassion Scale; SRNU: Self-reported Nicotine Use; UFEC: Utilization of Facility-based and Emergent Care.
Source: Study MAPP1 CSR Amendment, Section 9.5.2.3, and Study MAPP2 CSR, Section 9.5.2.3.

6.4 Statistical Analysis Plan (SAP)

6.4.1 Analysis of Primary Efficacy Data

The primary estimator of effects of randomized treatments was the difference between groups in mean change in CAPS-5 TSS from Baseline to 18 weeks after randomization in participants included in the mITT analysis set, which included all randomized participants who received investigational product in at least 1 medication session and completed at least 1 CAPS-5 assessment post-treatment. The de jure estimand of treatment efficacy, where CAPS-5 measures taken after treatment discontinuation were not included in the model, was used to estimate the causal effect of MDMA-AT on PTSD symptom severity in the intended population of patients with PTSD from any cause.

For the primary efficacy analysis, the treatment comparison was made at a 2-sided, 0.0499 level of alpha. As specified in the SAP, 0.001 of alpha was spent for the interim analysis. LS means from a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) was used to compare treatment groups at Week 18. The difference between treatment groups and the associated 95% confidence interval were calculated and presented at each visit. Missing data were not imputed, as specified in the de jure estimand.

6.4.2 Analysis of Secondary Efficacy Data

Change in the SDS Score from Baseline (Visit 3) to Primary Endpoint was the key secondary outcome measure and assessed by IR at Visit 3 and Visit 19 (18 weeks post Baseline).

For the key secondary analysis of efficacy, the de jure estimand was used and the statistical analysis was conducted using the same methodology as the primary efficacy measure but replacing Baseline CAPS-5 with Baseline SDS as a covariate in the model.

6.4.3 Analysis of Exploratory Efficacy Data

All analyses for exploratory objectives were assessed by the de jure estimand.

6.5 MAPP1 Study Results

6.5.1 MAPP1 Demographics

Key baseline demographics are presented in Table 8. The average age of participants was 43.6 years in the MDMA-AT group and 38.2 years in the placebo group. The majority of participants were female and White in both groups. Approximately 11% of participants in the MDMA-AT group and 7% in the placebo group were Hispanic or Latino.

Table 8: MAPP1 Baseline Demographics

	MDMA-AT N = 46 n (%)	Placebo + Therapy N = 44 n (%)
Sex, n (%)		
Male	19 (41.3)	12 (27.3)
Female[a]	27 (58.7)	32 (72.7)
Age, years		
Mean (SD)	43.6 (12.86)	38.2 (10.36)
Median (Min, Max)	39.10 (25, 71)	36.60 (21, 63)
Ethnicity, n (%)		
Hispanic or Latino	5 (10.9)	3 (6.8)
Not Hispanic or Latino	41 (89.1)	40 (90.9)
Race, n (%)		
American Indian or Alaska Native	3 (6.5)	0 (0.0)
Asian	2 (4.3)	5 (11.4)
Black or African American	0 (0.0)	2 (4.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)
White	39 (84.8)	30 (68.2)
Multiple	2 (4.3)	6 (13.6)

BMI: body mass index; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; SD: standard deviation

a. Two participants in the MDMA-AT group who were assigned female at birth identified their gender as non-binary.

Source: MAPP1 CSR Amendment; Tables 14.1.3, 14.1.4, 14.1.7, 14.2.1.1, 14.2.2.1, and 14.3.5.2

6.5.2 MAPP1 Disease Characteristics

MAPP1 participants' baseline PTSD characteristics are presented in Table 9. Average baseline CAPS-5 and SDS scores demonstrate the severity of participants' PTSD symptoms, with participants experiencing their PTSD for an average of approximately 14 years in both groups. Sertraline had been used at any time prior to the study by

approximately 26% and 23% of participants in the MDMA-AT and placebo groups, respectively. Paroxetine use prior to the study was reported in approximately 9% of MDMA-AT and placebo-treated participants, respectively.

Table 9: MAPP1 Participant PTSD Characteristics

	MDMA-AT N = 46 n (%)	Placebo + Therapy N = 44 n (%)
Trauma History, n (%)		
Veteran Status	10 (21.7)	6 (13.6)
Served in a combat area	6 (13.0)	5 (11.4)
Multiple trauma events	41 (89.1)	38 (86.4)
Developmental trauma events	40 (87.0)	36 (81.8)
Baseline PTSD Duration (years)		
Mean (SD)	14.8 (11.6)	13.3 (11.4)
Median (Min, Max)	12.61 (0.6, 48.8)	9.58 (0.7, 46.1)
Prior PTSD Medication, n (%)		
Sertraline	12 (26.1)	11 (25.0)
Paroxetine	4 (8.7)	4 (9.1)
Pre-study therapy, n (%)		
CBT	14 (30.4)	23 (52.3)
EMDR	24 (52.2)	14 (31.8)
Group therapy	21 (45.7)	14 (31.8)
Psychodynamic	12 (26.1)	11 (25.0)
DBT	2 (4.3)	2 (4.5)
Baseline CAPS-5 Total Severity Score		
Mean (SD)	44.0 (6.01)	44.2 (6.15)
Median (Min, Max)	43.5 (35, 57)	44.0 (35, 62)
Baseline CAPS-5 Dissociative Subtype, n (%)	6 (13.0)	13 (29.5)
Lifetime C-SSRS, n (%)[a]		
Presence of positive ideation	42 (91.3)	41 (93.2)
Serious ideation	20 (43.5)	17 (38.6)
Presence of positive behavior	16 (34.8)	13 (29.5)

CAPS-5: Clinician Administered PTSD Scale for DSM-5; CBT: Cognitive Behavioral Therapy; C-SSRS: Columbia Suicide Severity Rating Scale; DBT: Dialectical Behavior Therapy; EMDR: Eye Movement Desensitization and Reprocessing; PTSD: post-traumatic stress disorder; SD: standard deviation; SDS: Sheehan Disability Scale;
Lifetime accounts for all suicidal ideation and behavior prior to study, according to participant recall and medical records at Screening visit. According to the C-SSRS scoring guide, scores of four or five on the suicidal ideation category are considered serious ideation, and scores of one or greater are considered positive behavior or ideation.
Prior PTSD medication includes use of paroxetine and/or sertraline use at any time prior to screening.
Source: MAPP1 CSR Amendment, Tables 14.1.3.1 and 14.1.7

All participant reported a medical history of at least one co-morbid psychiatric disorder in addition to PTSD (Table 10). Of note, 91.3% of participants in the MDMA-AT group and 93.2% in the placebo group reported a history of suicidal ideation. Based on preferred term, 28.3% of participants in the MDMA-AT group and 18.2% in the placebo

group reported a medical history of alcohol use disorder and 15.2% and 13.6% (MDMA-AT and placebo groups, respectively) reported medical history of substance use disorder. Insomnia, nightmares, substance use disorder, depressive disorders, anxiety disorders, and suicidality are all commonly comorbid with PTSD (Colvonen et al, 2018; Jacobsen et al, 2001; Brady et al, 2000; Weathers et al, 2017).

Table 10: MAPP1 Participant Psychiatric History by Preferred Term (≥10% in Any Group)

System Organ Class Preferred Term	MDMA-AT N = 46 n (%)	Placebo + Therapy N = 44 n (%)
Psychiatric Disorders	**46 (100.0)**	**44 (100.0)**
Suicidal ideation	42 (91.3)	41 (93.2)
Major depression	42 (91.3)	40 (90.9)
Insomnia	38 (82.6)	31 (70.5)
Anxiety	26 (56.5)	20 (45.5)
Suicide attempt	16 (34.8)	10 (22.7)
Attention deficient/hyperactivity disorder	15 (32.6)	6 (13.6)
Nightmare	14 (30.4)	14 (31.8)
Social anxiety disorder	13 (28.3)	13 (29.5)
Generalized anxiety disorder	13 (28.3)	10 (22.7)
Intentional self-injury	12 (26.1)	7 (15.9)
Flashback	11 (23.9)	4 (9.1)
Hypervigilance	8 (17.4)	8 (18.2)
Panic disorder	7 (15.2)	6 (13.6)
Panic attack	6 (13.0)	10 (22.7)
Irritability	6 (13.0)	6 (13.6)
Alcohol use disorder	6 (13.0)	3 (6.8)
Suicidal behavior	5 (10.9)	10 (22.7)
Nicotine dependence	5 (10.9)	3 (6.8)
Depression	4 (8.7)	5 (11.4)
Obsessive-compulsive disorder	2 (4.3)	5 (11.4)

MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy
Source: MAPP1 CSR Amendment, Table 14.1.5.1

Medical history relevant to risk of CV disease is summarized in Table 11. The most frequent CV risk factors in the MDMA-AT treatment group were smoking (26.1%) and hyperlipidemia (23.9%).

Table 11: MAPP1 Participant Cardiovascular History

Cardiovascular Grouped Term	MDMA-AT N = 46 n (%)	Placebo + Therapy N = 44 n (%)
Smoking History[a]	12 (26.1)	8 (18.2)
Hyperlipidemia	11 (23.9)	2 (4.5)
Hypertension	5 (10.9)	3 (6.8)
Other Cardiac[b]	1 (2.2)	0 (0.0)
Diabetes/impaired glucose tolerance	1 (2.2)	1 (2.3)
Obesity	4 (8.7)	3 (6.8)

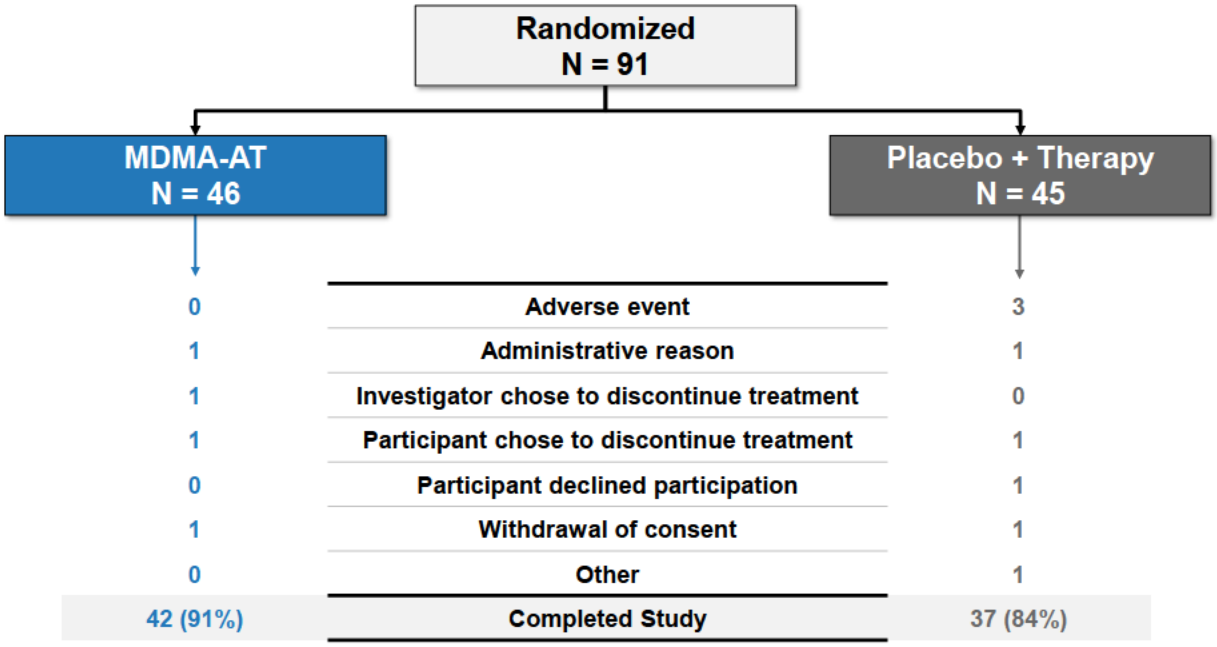
Medical history preferred terms are grouped into clinically relevant categories.
a. Includes current and former tobacco users.
b. One participant had an abnormal screening cardiac stress test that was considered not clinically significant.
Source: MAPP1 CSR Amendment, Table 14.1.5.1; MAPS_ADCOM_Tables_15APR24

6.5.3 MAPP1 Disposition

In total, 91 participants were randomized, 46 to MDMA-AT and 45 to placebo with identical therapy (Figure 11). One randomized participant withdrew consent prior to dosing in the placebo group. In total, 42 participants assigned to MDMA-AT and 37 participants assigned to placebo plus therapy completed the study. Study withdrawal and discontinuation were the primary reasons for missing data throughout the study.

To formally assess the range of possible impacts the missing data had on the primary efficacy analysis, several sensitivity analyses were performed (Appendix 11.3.1).

Figure 11: MAPP1 Participant Disposition

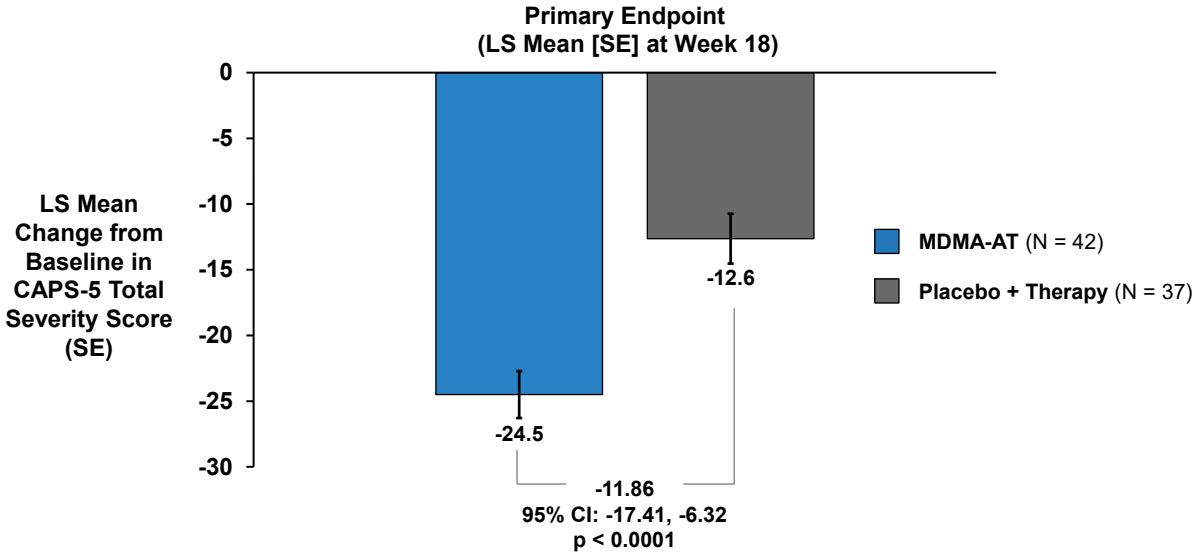


Source: MAPP1 CSR Amendment, Table 14.1.2 and 14.1.9

6.5.4 MAPP1 Primary Efficacy Endpoint Results: CAPS-5

In MAPP1, at Week 18, both treatment groups demonstrated clinically meaningful improvements in PTSD symptoms, as assessed by the LS mean change from baseline in the CAPS-5 TSS. The changes from baseline were 24.5 points and 12.6 points in the MDMA-AT and placebo with therapy groups, respectively. The difference between groups (11.86) was statistically significant ($p < 0.0001$) and favored the MDMA-AT group (Figure 12).

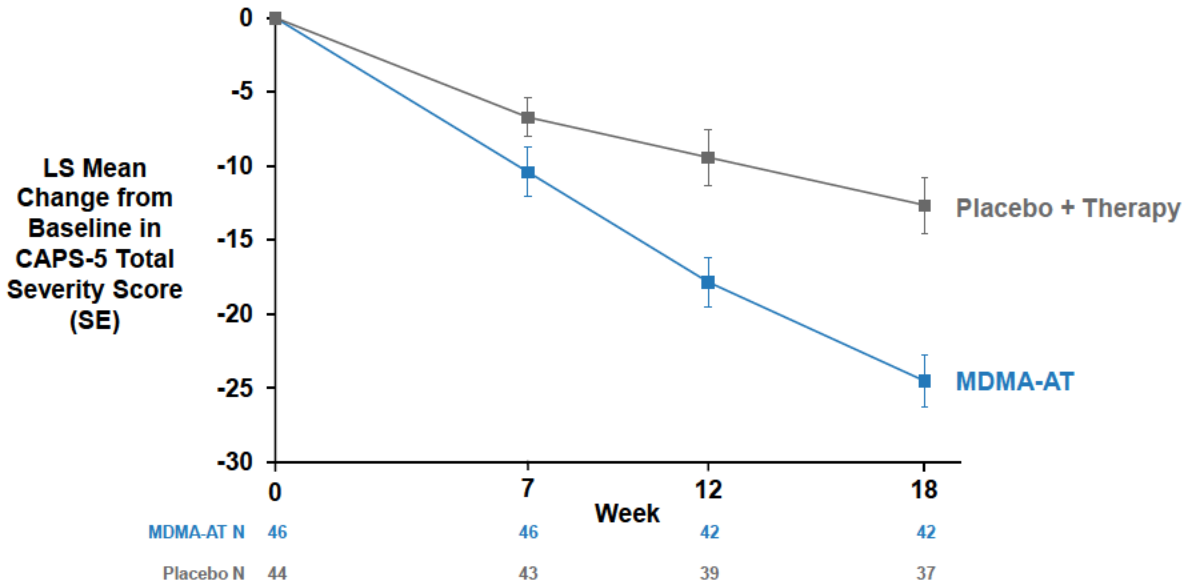
Figure 12: MAPP1 Primary Endpoint: Clinically Meaningful Improvement with Statistically Significant Difference between Groups in CAPS-5 TSS (mITT)



CAPS-5: Clinician-Administered PTSD Scale for DSM-5; LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SE: standard error
Note: Bars indicated ±1 SE
MMRM analysis uses all mITT participants.
Source: MAPP1 CSR Amendment, Table 14.2.1.1.1

A numerical difference between the treatment groups was apparent by the first timepoint, at Week 7 (following the first medication session) and increased at the subsequent timepoints (Figure 13).

Figure 13: MAPP1 LS Mean Change from Baseline in CAPS-5 TSS (mITT)

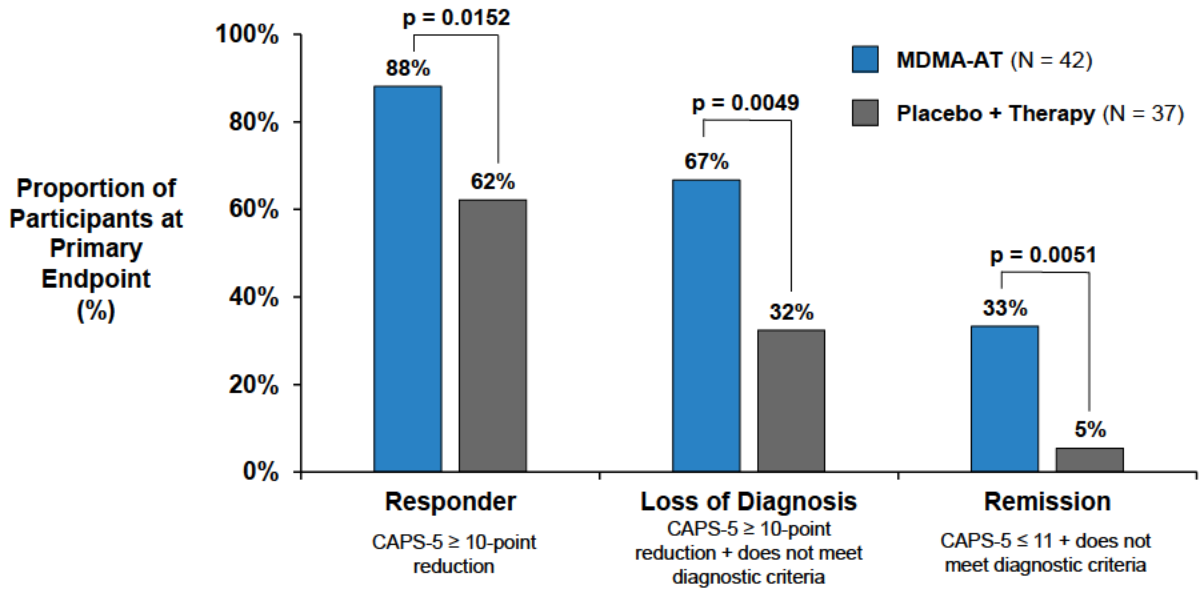


CAPS-5: Clinician-Administered PTSD Scale for DSM-5; LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SE: standard error; TSS: Total Severity Score
Source: MAPP1 CSR Amendment, Table 14.2.1.1.1

6.5.5 MAPP1 Responder Analysis of Primary Endpoint

A higher proportion of participants in the MDMA-AT group compared to the placebo group were classified via their CAPS-5 TSS at Week 18 as Responders (88.1% vs. 62.2%). Treatment differences were also observed for the more conservative CAPS-5 categories of Loss of Diagnosis (66.7% vs. 32.4%), and In Remission (33.3% vs. 5.4%), highlighting the clinically relevant benefit of MDMA-AT treatment (Figure 14).

Figure 14: MAPP1 MDMA-AT Associated with Greater Rates of Response, Loss of PTSD Diagnosis, and Remission vs Placebo (mITT)



CAPS-5: Clinician-Administered PTSD Scale for DSM-5; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; PTSD: post-traumatic stress disorder
Note: p-values shown are nominal and added for descriptive purposes.
Source: MAPP1 CSR Amendment Table 14.2.1.2

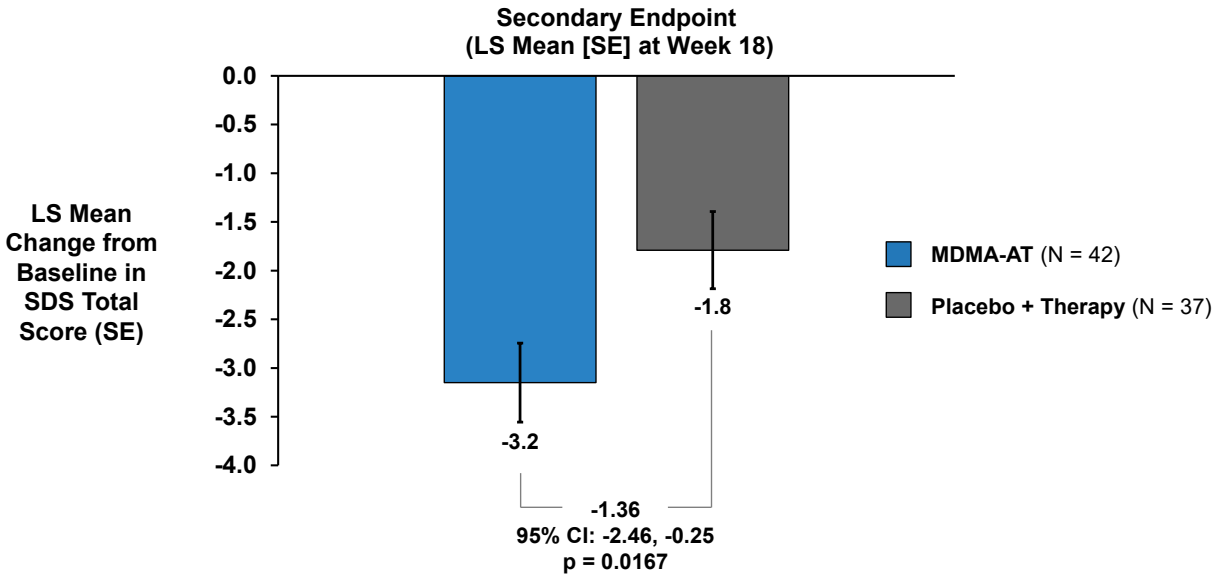
6.5.6 MAPP1 Primary Efficacy Endpoint Cumulative Responder Analysis

Figure 35 shows the cumulative responder percentages in the change from baseline to Week 18 of CAPS-5 TSS by treatment group. This figure demonstrates the differences in responder rates between the two groups for various levels of change from baseline, with consistently higher proportions of MDMA experiencing each level of change (e.g., 10-, 20-, 30-, and 40-point improvements from baseline).

6.5.7 MAPP1 Secondary Efficacy Endpoint Results: SDS

At Week 18, both treatment groups demonstrated improvements in functional impairment, with LS mean reductions in SDS of 3.2 points and 1.8 points in the MDMA-AT and placebo with therapy groups, respectively. The difference between groups (1.36) was statistically significant (p = 0.0167) and favored the MDMA-AT group (Figure 15).

Figure 15: MAPP1 Statistically Significant Improvement in SDS Total Score with MDMA-AT (mITT)



LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SDS: Sheehan Disability Scale
Note: Bars indicated ±1 SE
MMRM analysis uses all mITT participants.
Source: MAPP1 CSR Amendment Table 14.2.2.1

6.5.8 MAPP1 Responder Analysis of Secondary Endpoint

A higher proportion of participants in the MDMA-AT group compared to the placebo group met the SDS definition of responder (i.e., ≥ 4-point increase, 38.1% vs. 18.9%) and met the definition of In Remission (i.e., a score of ≤ 3 at endpoint, 42.9% vs. 13.5%).

6.5.9 MAPP1 Secondary Efficacy Endpoint Cumulative Responder Plot

Figure 36 shows the cumulative responder percentages in the change from baseline to Week 18 of SDS scores by treatment group. This figure demonstrates the differences in responder rates between the two groups for various levels of change from baseline. This display supplements the responder analysis (i.e., proportions of participants with a reduction of 4-points) to address the challenges of interpreting the results of the responder rates due to the FDA-requested modifications in SDS scoring (Section 6.3.2).

6.5.10 MAPP1 Exploratory Efficacy Analyses

An overall summary of the results of exploratory analyses in MAPP1 and MAPP2 is provided in Appendix 11.3.7. In general, the results were consistent with the primary and secondary efficacy results, including the subscales of the CAPS-5.

6.6 MAPP2 Study Results

6.6.1 MAPP2 Demographics

Participant baseline demographics are presented in Table 12. The average age of participants was 38.2 years in the MDMA-AT group and approximately 40 years in the placebo group. The majority of participants were female and White in both groups. Approximately 32% of participants in the MDMA-AT group and 22% in the placebo group were Hispanic or Latino.

Table 12: MAPP2 Baseline Demographics

	MDMA-AT N = 53 n (%)	Placebo + Therapy N = 51 n (%)
Gender, n (%)		
Male	21 (39.6)	9 (17.6)
Female	32 (60.4)	42 (82.4)
Age, years		
Mean (SD)	38.20 (11.02)	39.99 (9.60)
Median (Min, Max)	36.18 (21.3, 70.0)	38.22 (20.9, 66.0)
Ethnicity, n (%)		
Hispanic or Latino	17 (32.1)	11 (21.6)
Not Hispanic or Latino	36 (67.9)	39 (76.5)
Unknown	0 (0.0)	1 (2.0)
Race, n (%)		
American Indian or Alaska Native	0 (0.0)	2 (3.9)
Asian	5 (9.4)	6 (11.8)
Black or African American	5 (9.4)	3 (5.9)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (2.0)
White	37 (69.8)	32 (62.7)
Multiple	6 (11.3)	7 (13.7)

Max: maximum; MDMA: 3,4-methylenedioxymethamphetamine; Min: minimum; N: total number of participants; n: number of participants; SD: standard deviation.
Source: MAPP2 CSR, Table 14.1.3.1

6.6.2 MAPP2 Disease Characteristics

MAPP2 participants' baseline PTSD characteristics are presented in Table 13. MAPP2 included participants with at least moderate PTSD. The mean baseline CAPS-5 TSS was 39.4 in the MDMA-AT group and 38.7 in the placebo with therapy group. Participants in both groups reported having PTSD for approximately 16 years at Baseline. In the MDMA-AT group, approximately 28% of participants had used sertraline and 2% had used paroxetine before the study, compared to approximately 20% and 2%, respectively, in the placebo group.

Table 13: MAPP2 Participant PTSD Characteristics

	MDMA-AT N = 53 n (%)	Placebo + Therapy N = 51 n (%)
Trauma History, n (%)		
Veteran Status	9 (17.0)	7 (13.7)
Served in a combat area	9 (17.0)	6 (11.8)
Multiple trauma events	40 (75.5)	45 (88.2)
Developmental trauma events	49 (92.5)	43 (84.3)
Baseline PTSD Duration (years)		
Mean (SD)	16.25 (14.27)	16.14 (12.43)
Median (Min, Max)	10.14 (2.2, 51.5)	12.93 (1.2, 49.1)
Pre-study therapy, n (%)		
CBT	15 (28.3)	14 (27.5)
EMDR	17 (32.1)	18 (35.3)
Group therapy	9 (17.0)	15 (29.4)
Psychodynamic	15 (28.3)	11 (21.6)
DBT	4 (7.5)	2 (3.9)
Prior PTSD Medication, n (%)		
Sertraline	15 (28.3)	10 (19.6)
Paroxetine	1 (1.9)	1 (2.0)
Baseline CAPS-5 Total Severity Score		
Mean (SD)	39.4 (6.64)	38.7 (6.67)
Median (Min, Max)	39.0 (28, 55)	38.0 (28, 56)
Baseline Disease Severity (based on CAPS-5), n (%)		
Moderate (28-34)	13 (24.5)	15 (29.4)
Severe (≥ 35)	40 (75.5)	36 (70.6)
Baseline CAPS-5 Dissociative Subtype, n (%)	13 (24.5)	11 (21.6)

CAPS-5: Clinician-Administered PTSD Scale for DSM-5; Max: maximum; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; Min: minimum; N: total number of participants in each group; n: number of participants; PTSD: post-traumatic stress disorder; SD: standard deviation
Prior PTSD medication includes use of paroxetine and/or sertraline use at any time prior to screening.
Source: MAPP2 CSR, Table 14.1.3.1

Psychiatric disorders reported by participants in addition to PTSD are listed in Table 14. Overall, the most common psychiatric histories besides PTSD were major depression and suicidal ideation. In general, the psychiatric histories were similar in the MDMA-AT and placebo groups, except nightmare which was higher in MDMA-AT group than in the placebo group.

Table 14: MAPP2 Participant Psychiatric History by Preferred Term (≥10% in Any Group)

System Organ Class Preferred Term	MDMA-AT N = 53 n (%)	Placebo + Therapy N = 51 n (%)
Psychiatric disorders	53 (100.0)	51 (100.0)
Major depression	49 (92.5)	51 (100.0)
Suicidal ideation	44 (83.0)	47 (92.2)
Insomnia	36 (67.9)	34 (66.7)
Anxiety	29 (54.7)	26 (51.0)
Nightmare	27 (50.9)	18 (35.3)
Hypervigilance	20 (37.7)	21 (41.2)
Generalised anxiety disorder	17 (32.1)	13 (25.5)
Flashback	14 (26.4)	15 (29.4)
Intrusive thoughts	13 (24.5)	14 (27.5)
Intentional self-injury	11 (20.8)	15 (29.4)
Fear-related avoidance of activities	12 (22.6)	13 (25.5)
Social anxiety disorder	13 (24.5)	12 (23.5)
Attention deficit hyperactivity disorder	14 (26.4)	10 (19.6)
Suicide attempt	10 (18.9)	12 (23.5)
Panic attack	8 (15.1)	12 (23.5)
Irritability	9 (17.0)	9 (17.6)
Dissociation	10 (18.9)	7 (13.7)
Panic disorder	10 (18.9)	5 (9.8)
Alcohol use disorder	7 (13.2)	7 (13.7)
Binge eating	7 (13.2)	6 (11.8)
Drug abuse	7 (13.2)	3 (5.9)
Hyperarousal	4 (7.5)	6 (11.8)

MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; N: total number of participants in each group; n: number of participants
Source: MAPP2 CSR; Table 14.1.5.1

Medical history relevant to risk of CV disease is summarized in Table 15. The most frequent cardiovascular risk factors in the MDMA-AT treatment group were smoking (35.8%) and hyperlipidemia (22.6%).

Table 15: MAPP2 Participant Cardiovascular History

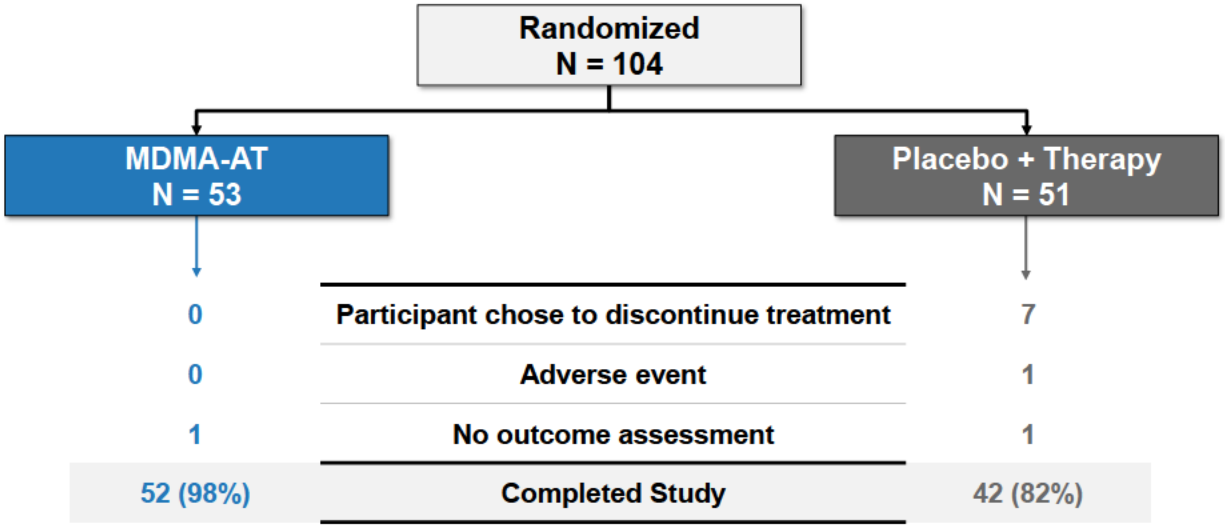
Cardiovascular Grouped Term	MDMA-AT N = 53 n (%)	Placebo + Therapy N = 51 n (%)
Smoking History[a]	19 (35.8)	14 (27.5)
Hyperlipidemia	12 (22.6)	7 (13.7)
Hypertension	5 (9.4)	1 (2.0)
Other Cardiac[b]	1 (1.9)	0 (0.0)
Diabetes/impaired glucose tolerance	3 (5.7)	2 (3.9)
Obesity	5 (9.4)	1 (2.0)

Medical history preferred terms are grouped into clinically relevant categories.
a. Includes current and former tobacco users
b. One participant had an abnormal screening stress echocardiogram that was considered not clinically significant.
Source: MAPP2 CSR, Table 14.1.5.2; MAPS_ADCOM_Tables_15APR24

6.6.3 MAPP2 Disposition

In total, 104 participants were randomized in the study (MDMA-AT: 53 participants; placebo: 51 participants) (Figure 16). In the MDMA-AT group, 52 participants completed the study and in the placebo group 43 participants completed the study. All 53 participants randomized to MDMA-AT and 43 participants in the placebo arm completed all 3 medication sessions.

Figure 16: MAPP2 Participant Disposition

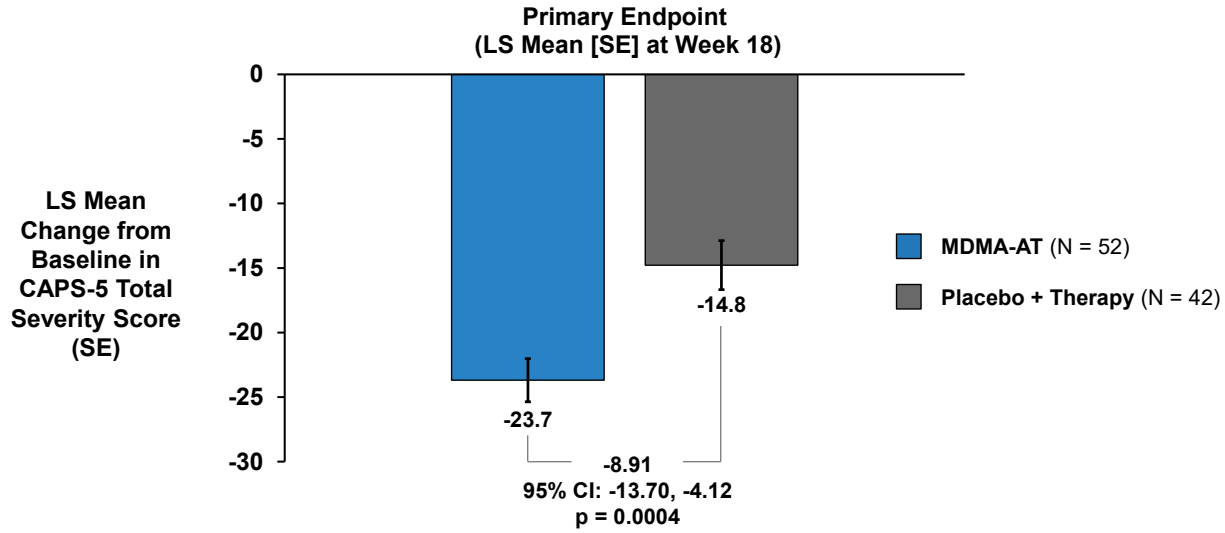


Note: One participant in the MDMA-AT group did not complete a CAPS-5 assessment at Week 18 but completed all three medication sessions. One participant in the Placebo group did not complete any outcome assessments after receiving placebo in the first medication session and was excluded from the modified intent-to-treat.
Source: MAPP2 CSR, Table 14.1.2

6.6.4 MAPP2 Primary Efficacy Endpoint Results: CAPS-5

At primary endpoint, both treatment groups demonstrated clinically meaningful improvements in PTSD symptoms, with LS mean reductions in CAPS-5 TSS of 23.7 points and 14.8 points in the MDMA-AT and placebo with therapy groups, respectively. The difference between groups (8.91) was statistically significant (p = 0.0004) and favored the MDMA-AT group (Figure 17).

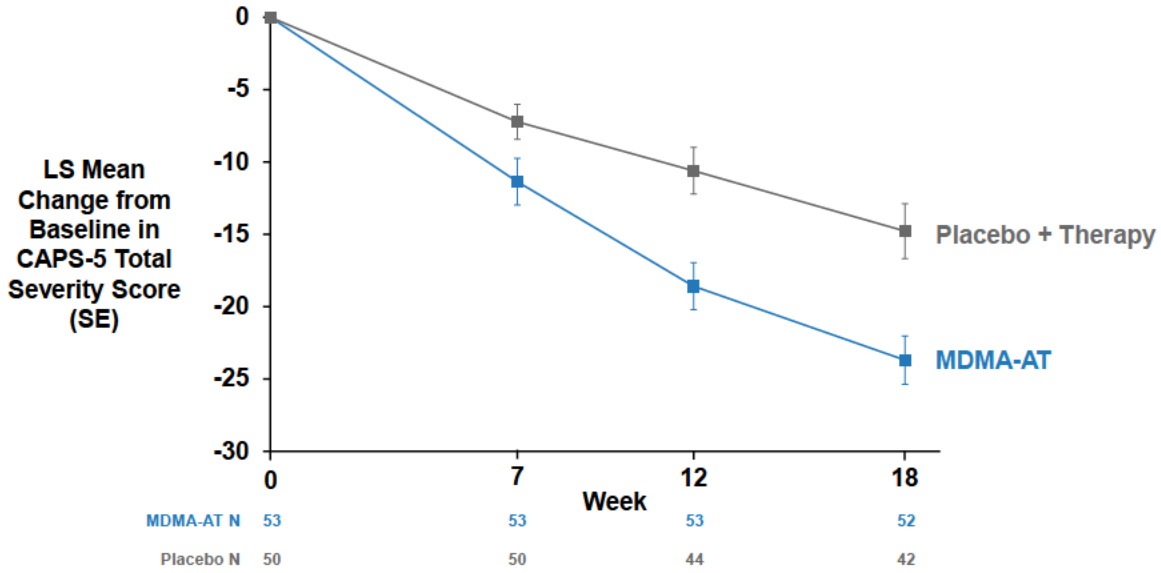
Figure 17: MAPP2 Primary Endpoint: Clinically Meaningful Improvement with Statistically Significant Difference between Groups in CAPS-5 TSS (mITT)



CAPS-5: Clinician-Administered PTSD Scale for DSM-5; LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SE: standard error
Note: Bars indicated ±1 SE
MMRM analysis uses all mITT participants.
Source: MAPP2 CSR, Table 14.2.1.1.1

A numerical difference between the treatment groups was apparent by the first timepoint, at Week 7 (following the first medication session), and the numerical treatment difference increased at the subsequent timepoints (Figure 18).

Figure 18: MAPP2 LS Mean Change from Baseline in CAPS-5 TSS (mITT)

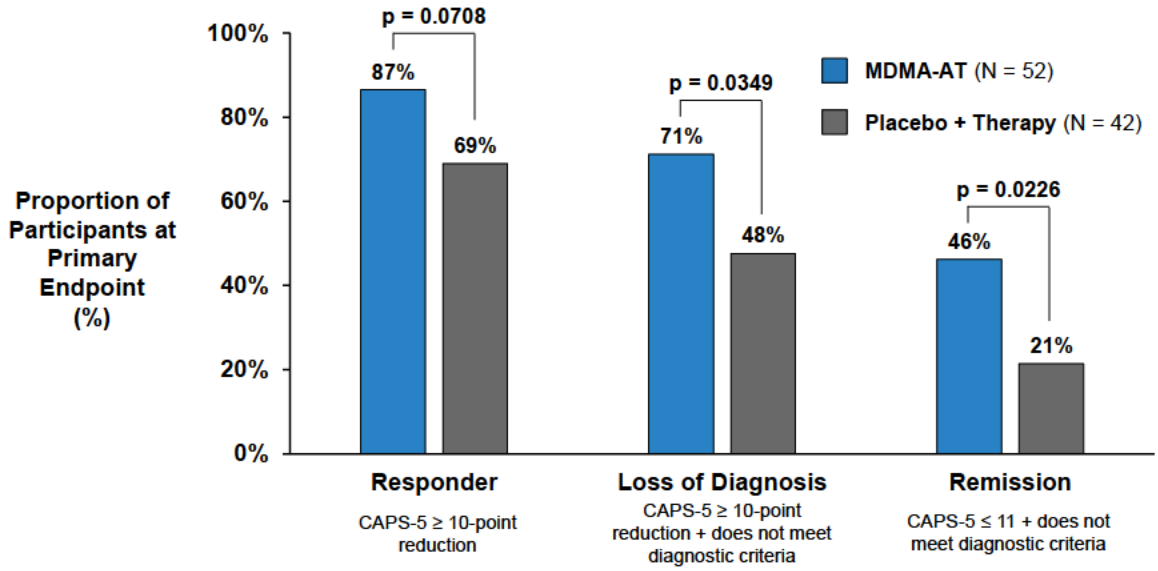


CAPS-5: Clinician-Administered PTSD Scale for DSM-5; LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SE: standard error; TSS: Total Severity Score
MMRM analysis uses all mITT participants.
Source: MAPP2 CSR, Table 14.2.1.1.1

6.6.5 MAPP2 Responder Analysis of Primary Endpoint

A higher proportion of participants in the MDMA-AT group compared to the placebo group were classified via their CAPS-5 TSS at Week 18 as Responders (86.5% vs. 69.0%). Treatment differences were also observed for the more conservative CAPS-5 defined categories of Loss of Diagnosis definition (71.2% vs. 47.6%), and In Remission (46.2% vs. 21.4%), highlighting the clinically relevant benefit of MDMA-AT treatment (Figure 19).

Figure 19: MAPP2 Greater Rates of Treatment Response, Loss of PTSD Diagnosis, and Remission in MDMA-AT Group Participants (mITT)



CAPS-5: Clinician-Administered PTSD Scale for DSM-5; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; PTSD: post-traumatic stress disorder
Note: p-values shown are nominal and added for descriptive purposes.
Source: MAPP2 CSR, Table 14.2.1.2

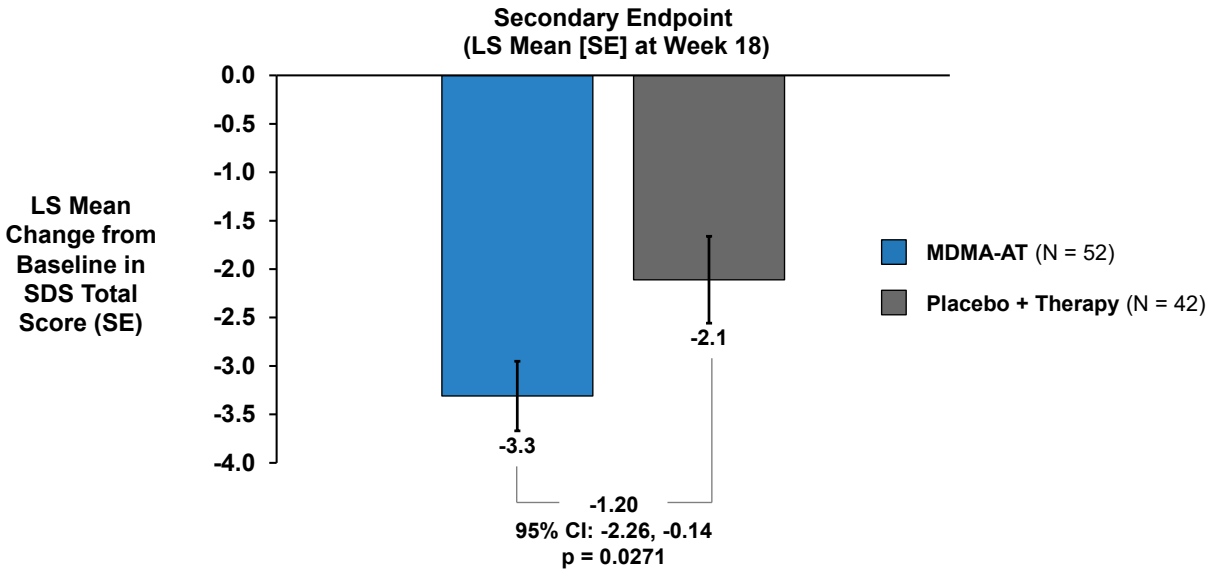
6.6.6 MAPP2 Primary Efficacy Endpoint Cumulative Responder Analysis

Figure 37 shows the cumulative responder percentages in the change from baseline to Week 18 of CAPS-5 TSS by treatment group. This figure demonstrates the differences in responder rates between the two groups for various levels of change from baseline, with consistently higher proportions of MDMA experiencing each level of change (e.g., 10-, 20-, 30-, and 40-point improvements from baseline).

6.6.7 MAPP2 Secondary Efficacy Endpoint Results: SDS

At Week 18, both treatment groups demonstrated improvements in functional impairment, with LS mean reductions in SDS of 3.3 points and 2.1 points in the MDMA-AT and placebo with therapy groups, respectively. The difference between groups (1.20) was statistically significant (p = 0.0271) and favored the MDMA-AT group (Figure 20).

Figure 20: MAPP2 Key Secondary Endpoint Demonstrated Functional Improvements (mITT)



LS: least squares; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; mITT: modified intent-to-treat; SDS: Sheehan Disability Scale
Note: Bars indicated ±1 SE
MMRM analysis uses all mITT participants.
Source: MAPP2 CSR, Table 14.2.2.1

6.6.8 MAPP2 Responder Analysis of Secondary Endpoint

A higher proportion of participants in the MDMA-AT group compared to the placebo group met the SDS definition of responder (i.e., ≥ 4-point decrease, 53.8% vs. 19.0%) and met the definition of In Remission (i.e., a score of ≤ 3 at endpoint, 55.8% vs. 40.5%).

6.6.9 MAPP2 Secondary Efficacy Endpoint Cumulative Responder Plot

Figure 38 shows the cumulative responder percentages in the change from baseline to Week 18 of SDS scores by treatment group. This figure demonstrates the differences in responder rates between the two groups for various levels of change from baseline. This display supplements the responder analysis (i.e., proportions of participants with a reduction of 4-points) to address the challenges of interpreting the results of the responder rates due to the FDA-requested modifications in SDS scoring (Section 6.3.2).

6.6.10 MAPP2 Exploratory Efficacy Analyses

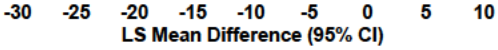
An overall summary of the results of exploratory analyses in MAPP1 and MAPP2 is provided in Appendix 11.3.7. In general, the results were consistent with the primary and secondary efficacy results, including the subscales of the CAPS-5.

6.7 MAPP1 and MAPP2 Pooled Subgroup Analysis Results

Figure 21 summarizes the CAPS-5 TSS change from baseline to Week 18 in various subgroups. Results should be interpreted with caution in subgroups with a small number of participants; however, the LS mean difference was in favor of MDMA-AT treatment in all subgroups, including the subgroups of moderate and severe disease by the baseline CAPS-5 TSS.

Figure 21: Treatment Estimates (CAPS-5 TSS CFB to Week 18) by Subgroup – De Jure Estimand (Pooled Phase 3 mITT Population)

Subgroup		MDMA n	Placebo n	LS Mean Difference (95% CI)
Overall		94	79	-9.7 (-13.2, -6.1)
Age	18 - < 50 years	73	67	-9.3 (-13.4, -5.3)
	≥ 50 years	21	12	-5.7 (-16.7, 5.3)
Sex	Female	56	62	-8.5 (-12.9 -4.1)
	Male	38	17	-12.3 (-19.5, -5.0)
Race	Non-White	21	27	-6.3 (-13.0, -0.5)
	White	73	51	-12.7 (-17.1, -8.3)
Ethnicity	Hispanic or Latino	20	12	-11.6 (-21.5, -1.7)
	Not Hispanic or Latino	74	65	-9.1 (-13.3, -5.0)
BMI	< 30 kg/m²	77	68	-9.3 (-13.2, -5.5)
	≥ 30 kg/m²	17	11	-11.3 (-20.6, -1.0)
Dissociative Subtype	Yes	18	20	-16.1 (-23.9, -8.3)
	No	76	59	-8.7 (-12.8, -4.7)
Overnight Stay	Yes	71	61	-10.2 (-14.4, -5.9)
	No	23	15	-7.0 (-14.0, 0.0)
Baseline Severity	Moderate	13	12	-10.0 (-19.1, -1.0)
	Severe	81	67	-9.5 (-13.4, -5.6)



CAPS-5: Clinician-Administered PTSD Scale for DSM-5; CFB: change from baseline; mITT: modified intent-to-treat; TSS: total severity score.
Source: Summary of Clinical Efficacy, Figure 14.3.2

6.8 MPLONG Study Design

Eligible participants were strongly encouraged to participate in a separate LTFU study, MPLONG, in which the follow-up assessments were to occur at least 6 months after the last treatment in the parent study.

MPLONG was a multi-center, non-interventional, observational LTFU study of MDMA-AT. No study drug or therapy was administered in this study. All participants were informed about the MPLONG study as a part of a parent study (MAPP1, MAPP2, MP16, MP17, or MAPPUSX). The primary evidence for the durability of the treatment response (i.e., persistence of effectiveness following acute treatment) comes from the Phase 3 (MAPP1 and MAPP2) participants who enrolled in MPLONG.

MPLONG opened for enrollment after the MAPP1 parent study had finished, the database had been locked, and participants had been unblinded to treatment assignment. Therefore, enrollees from MAPP1 entered MPLONG knowing whether they had received MDMA-AT or placebo in the parent study. Participants who entered

MPLONG after having completed MAPP2 remained blinded to treatment assignment until the MAPP2 database was locked and they had completed participation in MPLONG.

Data were collected on effectiveness (CAPS-5) and functional impairment (SDS) by an IR, as in the parent studies. Additionally, the study collected health economics and a subset of safety data, including interim medical history, interim medications, interim psychotherapy, illicit MDMA use, and suicidality since the parent study. The data were collected at multiple visits conducted within a single window of time to reduce assessment fatigue in participants.

6.8.1 MPLONG Enrollment Criteria

Inclusion criteria were as follows:

1. Enrolled in a sponsored study of MDMA-AT for the treatment of PTSD.
2. Had received investigation medicinal product (IMP) in at least one medication session in the parent study.
3. Agreed to be contacted by study team approximately 6 months after the last medication session in the parent study to schedule and participate in LTFU Visit.

Exclusion criteria were as follows:

1. Unable to give adequate informed consent.
2. Had any current problem which, in the opinion of the investigator or medical monitor, might interfere with participation.

6.9 MPLONG Study Results

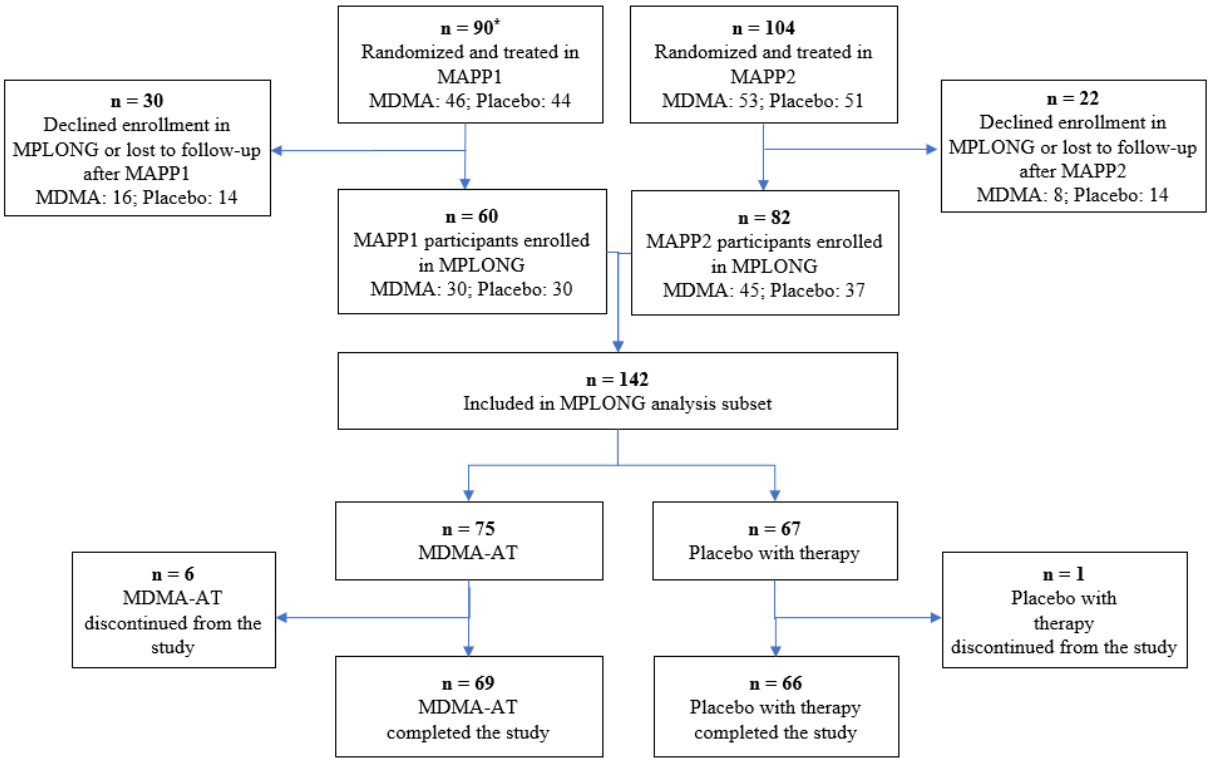
MPLONG results are presented for the MAPP2 study participants who were still blinded at the time of MPLONG assessments, followed by pooled results for MAPP1 and MAPP2 participants.

6.9.1 MPLONG Disposition

The number of participants from the Phase 3 parent studies (MAPP1 and MAPP2) who enrolled in MPLONG and were included in the analysis subset is presented in Figure 22.

In total, 60 out of the 90 participants from MAPP1 (67%) enrolled (MDMA-AT: 30; placebo: 30) and 82 out of the 104 participants from MAPP2 (79%) enrolled (MDMA-AT: 45; placebo: 37) in the MPLONG study. Of the 75 participants in the MDMA-AT group, 69 completed the study and 66 of the 67 participants in the placebo group completed the study, i.e., completed all assessments.

Figure 22: MPLONG Participant Disposition (MAPP1 and MAPP2)



MDMA-AT: 3,4-methylenedioxymethamphetamine assisted therapy; n = number of participants
*91 participants in MAPP1 were initially randomized, however, 1 participant who was randomized declined dosing on the morning of the medication session.
Sources: MAPP1 Table 14.1.1, MAPP2 Table 14.1.1, MPLONG Table 14.1-1.2, MPLONG Table 14.1-2.1, and MPLONG Table 14.1-2.2

6.9.2 MPLONG Demographics

Demographics and Baseline characteristics for the mITT subset are summarized in Table 16 for all MAPP1 and MAPP2 participants enrolled in MPLONG. The mITT subset includes all MPLONG participants who were initially enrolled in MAPP1 or MAPP2, received any study drug in the parent study, and completed a post-treatment outcome measure in the parent study. Results are presented by treatment assignment in the parent study. Baseline characteristics, unless otherwise indicated, are those collected in the parent study.

Table 16: MPLONG Baseline Demographics (MAPP1, MAPP2)

Characteristic	MDMA-AT N = 75	Placebo + Therapy N = 67
Age (years), n		
Mean (SD)	41.4 (13.09)	39.4 (10.42)
Median (min, max)	38.0 (21,71)	37.2 (21, 66)
Gender, n (%)		
Male	32 (42.7)	17 (25.4)
Female	43 (57.3)	50 (74.6)
Ethnicity, n (%)		
Hispanic or Latino	18 (24.0)	9 (13.4)
Not Hispanic or Latino	57 (76.0)	57 (85.1)
Unknown	0 (0.0)	1 (1.5)
Race, n (%)		
American Indian or Alaska Native	3 (4.0)	2 (3.0)
Asian	6 (8.0)	6 (9.0)
Black or African American	5 (6.7)	5 (7.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.5)
White	54 (72.0)	42 (62.7)
Not Reported	0 (0.0)	1 (1.5)
Multiple	7 (9.3)	10 (14.9)

MDMA: 3,4-methylenedioxymethamphetamine; n: number of participants; N: total number of participants
Percentages are calculated using the number of participants in each treatment group as the denominator. Participant demographic and Baseline characteristics were collected from the parent study.
Source: MPLONG CSR Interim, Table 14.1-4.1

6.9.3 MPLONG Disease Characteristics

Psychiatric history for the mITT subset (MAPP1 and MAPP2 participants), including the trauma history and Baseline Adverse Childhood Experience (ACE), Beck Depression Inventory II (BDI-II), and CAPS-5 TSS as collected at baseline in the parent study, are presented in Table 17. The mean durations of follow-up from the parent study to MPLONG follow-up in the MDMA-AT and placebo groups were 15.9 months and 15.8 months, respectively. Of note, as expected, the CAPS-5 scores at the parent study termination visit were lower in the MDMA-AT treatment group compared to participants that had been previously treated with placebo (15.9 vs 24.9), as were the SDS scores (3.0 vs 4.3).

Table 17: MPLONG Participant Characteristics (MAPP1, MAPP2)

Characteristic	MDMA-AT N = 75	Placebo + Therapy N = 67
MPLONG duration of follow-up, mean (months)		
Mean	15.9	15.8
Median (min, max)	12.7 (6.1, 32.7)	12.7 (6.0, 32.9)
Trauma History, n (%)		
Veteran Status	14 (18.7)	11 (16.4)
Served in combat area	12 (16.0)	10 (14.9)
Multiple trauma events	59 (78.7)	60 (89.6)
Developmental trauma events	68 (90.7)	56 (83.6)
Baseline PTSD duration (years)		
Mean (SD)	16.76 (13.98)	14.42 (11.83)
Median (min, max)	11.80 (0.8, 51.5)	10.28 (1.1, 49.1)
Prior PTSD medication, n (%)		
Paroxetine	4 (5.3)	3 (4.5)
Sertraline	25 (33.3)	11 (16.4)
Baseline CAPS-5 Total Severity Score		
Mean (SD)	40.3 (6.05)	40.9 (6.70)
Median (min, max)	40.0 (29, 57)	40.0 (28, 62)
Baseline disease severity (based on CAPS-5), n (%)		
Moderate (28-34)	11 (14.7)	9 (13.4)
Severe (≥35)	64 (85.3)	58 (86.6)
Baseline CAPS-5 Dissociative Subtype		
No	61 (81.3)	50 (74.6)
Yes	14 (18.7)	17 (25.4)
Study termination CAPS-5 Total Severity Score [a]		
Mean (SD)	15.9 (12.55)	24.9 (12.31)
Median (min, max)	14.0 (0, 44)	26.0 (2, 48)
Baseline SDS Total Score		
Mean (SD)	6.2 (1.81)	6.6 (1.78)
Median (min, max)	6.7 (1, 10)	6.3 (3, 10)
Study termination SDS Total Score[a]		
Mean (SD)	3.0 (2.77)	4.3 (2.63)
Median (min, max)	2.5 (0, 9)	4.7 (0, 9)
Baseline ACE Total Score		
Mean (SD)	4.9 (2.85)	4.8 (2.82)
Median (min, max)	5.0 (0, 10)	5.0 (0, 10)
Baseline BDI-II Total Score		
Mean (SD)	27.1 (12.72)	29.0 (11.43)

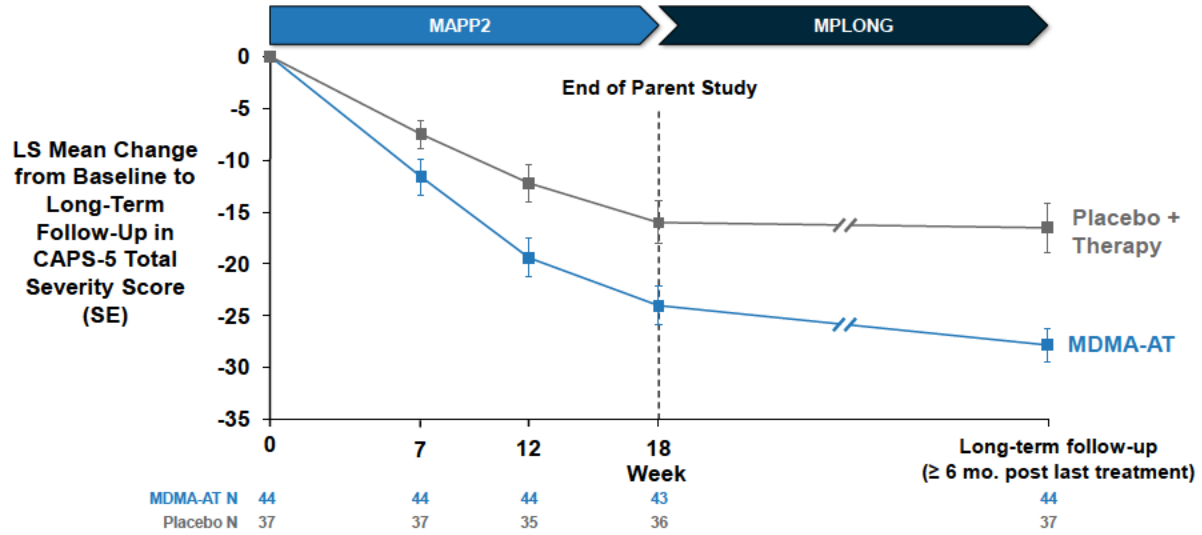
Characteristic	MDMA-AT N = 75	Placebo + Therapy N = 67
Median (min, max)	27.0 (3, 53)	30.0 (4. 50)

ACE: adverse childhood experiences; BDI-II: Beck depression inventory-II; CAPS-5: clinician-administered PTSD scale for DSM-5; MDMA: 3,4-methylenedioxymethamphetamine; mITT: modified intent to treat;
n: number of participants; N: total number of participants; PTSD: posttraumatic stress disorder;
SDS: Sheehan disability scale
Prior PTSD medication includes use paroxetine and/or sertraline use at any time prior to the parent study.
Percentages are calculated using the number of participants in each treatment group as the denominator.
Participant demographic and Baseline characteristics were collected from the parent study.
a. Last available assessment in the parent study.
Source: MPLONG CSR Interim, Table 14.1-4.1

6.9.4 MPLONG Primary Endpoint Results

Figure 23 presents the change from the parent study baseline CAPS-5 TSS for the effectiveness subset, i.e., participants who completed a follow-up PTSD endpoint assessment in MPLONG. The results for participants who enrolled in MPLONG from the MAPP2 study are presented. The differences between the treatment groups observed during the parent study persisted to the long-term follow-up visit, which occurred at least 6 months after the last medication session.

Figure 23: MPLONG Change from Parent Study Baseline in CAPS-5 Total Severity Score (Effectiveness Subset; MAPP2)

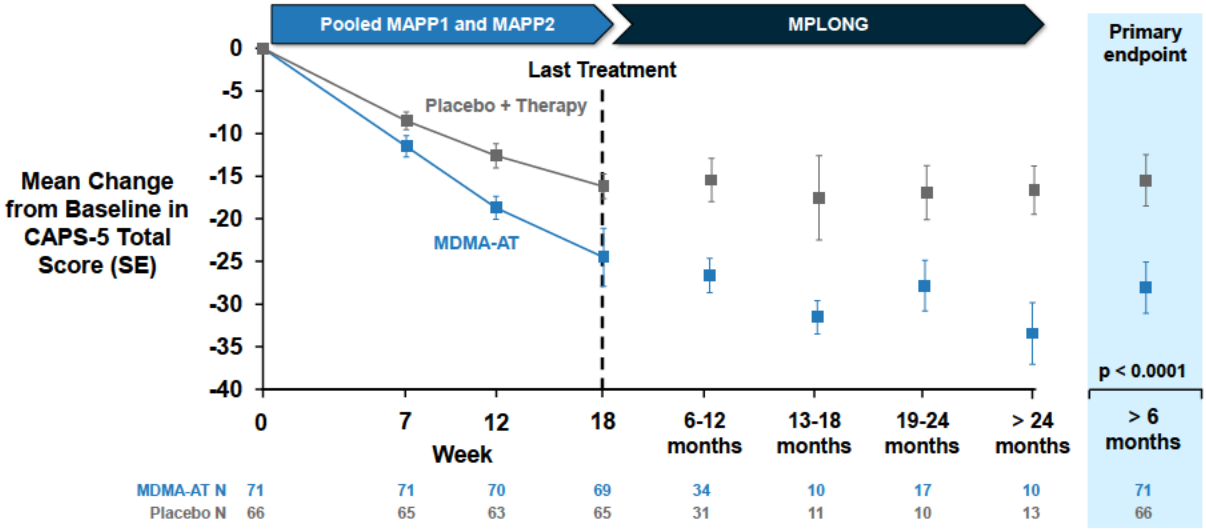


Effectiveness subset: all participants who completed a follow-up PTSD endpoint assessment.
Source: MPLONG CSR Interim, Table 14.2-5.1/2/3

A similar separation between the treatment groups was observed when MPLONG CAPS-5 TSS data for participants from both MAPP1 and MAPP2 parent studies were pooled (Figure 24). Similar differences between the treatment groups were observed for participants who had the MPLONG follow-up visit between 6 and 12 months, 13 -18 months, 19-24 months and >24 months.

These data provide evidence of durability of treatment effect in participants who enrolled in MPLONG at least 6 months after the last medication session in the parent study.

Figure 24: MPLONG Change from Phase 3 Parent Study Baseline in CAPS-5 Total Severity Score (Effectiveness Subset; MAPP1 and MAPP2) – Time Since Treatment Subgroups

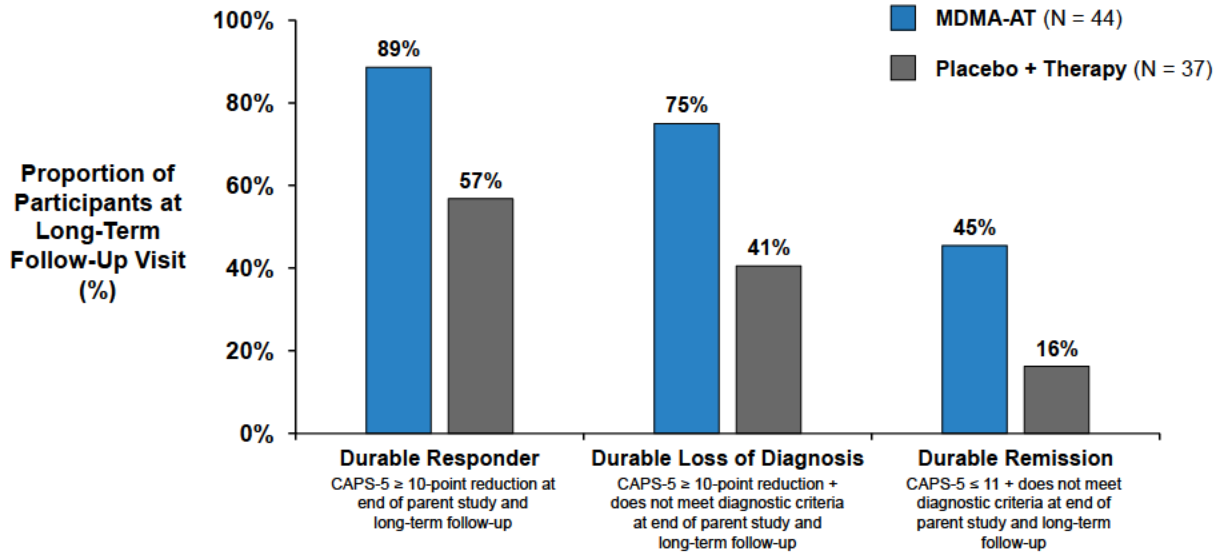


CAPS-5: Clinician Administered PTSD Scale for DSM-5; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; SE: standard error
Effectiveness subset: all participants who completed a follow-up PTSD endpoint assessment
For the follow-up duration categories, each participant is including in one visit window only (e.g., 6-12 months, 13-18 months, 19-24 months, >24 months). The sum of the numbers of participants in each of the follow-up duration categories in the placebo group is 65 as one participant with a follow-up duration of 1 day < 6 months was not included in the 6-12 month visit window.
Note: p-values shown are nominal and added for descriptive purposes.
Source: MPLONG CSR Interim, Table 14.2-2.3

6.9.5 MPLONG Responder Analysis of Primary Endpoint

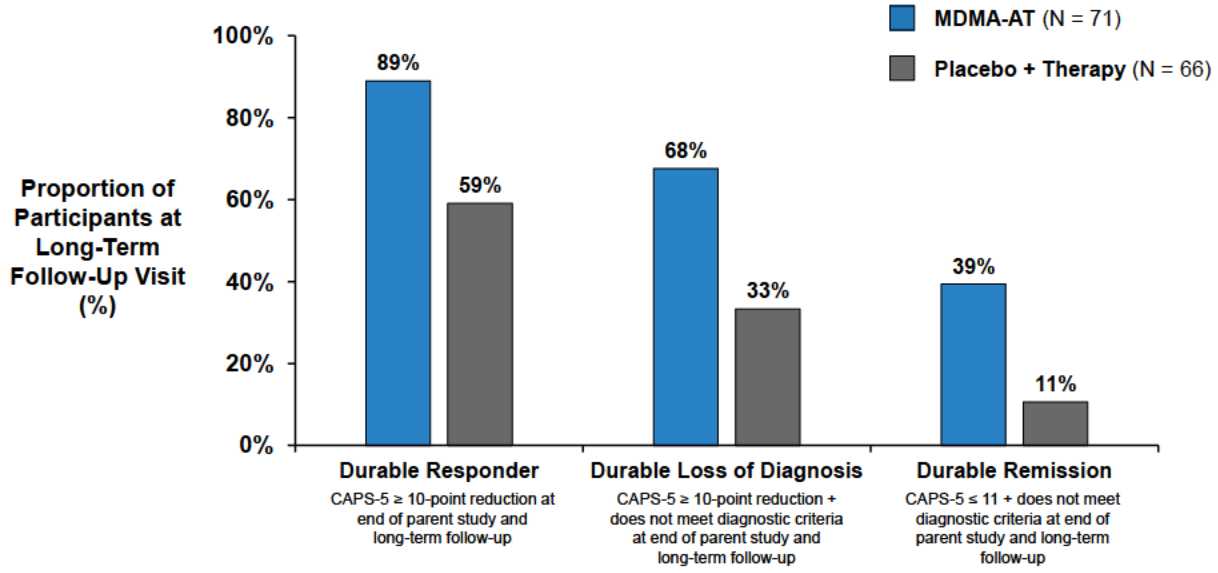
Consistent with the primary endpoint responder analysis results in MAPP1 and MAPP2, a higher proportion of participants in the MDMA-AT group compared to the placebo group still met the definition of Responder, Loss of Diagnosis, and Remission at LTFU. These results were consistent for both the participants who were still blinded during MPLONG (from parent study MAPP2; Figure 25), as well as for the combined data of participants from parent studies MAPP1 and MAPP2 (Figure 26).

Figure 25: MPLONG Responder Analysis – Persistence of Effectiveness at the Long-Term Follow Up Visit (Effectiveness Subset; MAPP2)



Effectiveness subset: all participants who completed a follow-up PTSD endpoint assessment.
Source: MPLONG CSR Interim, Table 14.2-10.2

Figure 26: MPLONG Responder Analysis – Persistence of Effectiveness at the Long-Term Follow-Up Visit (Effectiveness Subset; MAPP1 and MAPP2)



APS-5: Clinician Administered PTSD Scale for DSM-5; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy
Effectiveness subset: all participants who completed a follow-up PTSD endpoint assessment
Source: MPLONG CSR Interim, Table 14.2-10.1 Final

In summary, results from the MPLONG study provide evidence of durability of the treatment effect of MDMA-AT on CAPS-5 TSS observed at the end of MAPP1 and

MAPP2 through the LTFU period. The CAPS-5 results were similar regardless of the duration of follow-up from the last parent study medication session to the MPLONG CAPS-5 assessment, including participants who had LTFU within one year compared to LTFU done >12 months after the parent study.

Additional data supporting the long-term treatment effect of MDMA-AT from the Sponsor's Phase 2 program is provided in Appendix 11.4.

6.10 Efficacy Conclusions

The adequate and well-controlled Phase 3 studies demonstrated statistically significant and clinically meaningful differences between the MDMA-AT group and the placebo with therapy group in the primary and key secondary endpoints, and, therefore, met the evidentiary standard for demonstration of efficacy. Treatment benefit was demonstrated in overall improvement in PTSD symptom severity, as assessed by an accepted endpoint for demonstration of efficacy in this indication, the CAPS-5 TSS. A numerical difference in both the CAPS-5 TSS with MDMA-AT compared to placebo was seen by Week 7 and increased at subsequent timepoints. There was also a greater proportion of participants in the MDMA-AT group than in the placebo group who met the CAPS-5 definitions of Responder, Loss of PTSD Diagnosis and In Remission, demonstrating the clinical relevance of the treatment benefit.

Improvement in functional impairment was assessed by the key secondary endpoint, SDS and also demonstrated a statistically significant difference from placebo, which further supports the treatment benefit.

Supportive evidence of long-term efficacy for MDMA-AT comes from the LTFU non-interventional study MPLONG which evaluated evidence of durability of the treatment effect after acute treatment with MDMA-AT at ≥ 6 months following the last medication session in the parent study.

Overall, there is substantial evidence of effectiveness for acute treatment with MDMA-AT for the treatment indication of PTSD in a representative population of patients with moderate to severe PTSD.

7 CLINICAL SAFETY

Summary

- The focus of safety in this briefing document is on pooled data from the Phase 3, placebo-controlled, MAPP1 and MAPP2 studies (Phase 3 Pool; Safety Set).
- MDMA-AT was generally well-tolerated, with few discontinuations due to AEs. Most AEs were mild to moderate, transient, and self-limiting.
- The most-frequent treatment-related TEAEs were consistent with the mechanism of action of MDMA.
- No deaths were reported in the pooled Phase 3 studies. There were 2 deaths in the Phase 2 studies. Both occurred more than 6 months after the completion of dosing and were considered by the Sponsor and the investigator to be not related to study drug.
- The Sponsor has proposed mitigation strategies for the identified and potential risks of MDMA-AT, both observed and theoretical. These planned strategies have been integrated into a safe-use framework currently under development by the Sponsor in consultation with FDA.

The safety of MDMA-AT in the treatment of PTSD is supported by safety data from 17 clinical studies with 427 participants exposed to MDMA, including 287 participants with PTSD and 140 healthy volunteers. Pooled analyses were conducted on safety data from six Phase 2 and Phase 3 studies (MDMA-AT: n = 226; placebo: n = 95); the remaining studies were not pooled (Appendix 11.1).

The focus of safety in this briefing document is on pooled data from the Phase 3, placebo-controlled MAPP1 and MAPP2 studies (Pooled Phase 3; Safety Set), as they provide the best assessment of the safety profile of MDMA-AT in comparison to placebo in blinded studies, in the target patient population, who have been treated with the intended dosing regimen.

A total of 194 participants are included in this pooling group, with 99 participants in the MDMA-AT group and 95 participants in the placebo with therapy group.

7.1 Disposition of Participants

Disposition of participants in the Phase 3 pool is presented in Table 18. Overall, 94.9% of participants in the MDMA-AT group and 84.2% of participants in the placebo group completed the studies. The most common primary reason for early termination was participant choice and AE. There were no AEs leading to death.

One participant (1.0%) in the MDMA-AT group who terminated early due to participant choice had an AE as a secondary reason for early discontinuation. Two participants

(2.0%) in the placebo group who terminated early due to participant choice had an AE as a secondary reason for early discontinuation.

Table 18: Participant Disposition (Pooled Phase 3; Safety Set)

Studies Disposition	MDMA-AT N = 99 n (%)	Placebo + Therapy N = 95 n (%)
Completed Study	94 (94.9)	80 (84.2)
Early Termination	5 (5.1)	15 (15.8)
Primary Reason for Early Termination		
Adverse Event or Death[a]	0 (0.0)	4 (4.2)
Protocol Deviation	0 (0.0)	0 (0.0)
Administrative Reason	1 (1.0)	1 (1.1)
Investigator Chose to Discontinue Treatment	1 (1.0)	0 (0.0)
Participant Chose to Discontinue Treatment	2 (2.0)	8 (8.4)
Withdrawal of Consent	1 (1.0)	1 (1.1)
Lost to Follow-up	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.1)
COVID-19 Related	0 (0.0)	1 (1.1)

COVID-19: Coronavirus disease 2019; IMP: investigational medicinal product; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy
Participants who completed the study also completed study treatments; however, a participant may have completed 3 medication sessions and then discontinued from the study.
Percentages are calculated using the number of participants in each treatment group (N) as the denominator.
Early Termination includes participants that discontinued intervention and those that completed 3 medication sessions but did not complete the study. Of the 5 participants who terminated early, 2 participants in MAPP1 may have completed additional integration visits after IMP termination and the remaining 3 participants (2 participants from MAPP1 and 1 participant from MAPP2) did not.
Only the primary reason for study termination is summarized in the table.
a. No participants died during the study.
Source: ISS, Table 14.1.1.5

7.2 Treatment Exposure

The MDMA-AT treatment group includes all participants who received one or more doses of 80 mg or 120 mg MDMA as the first part of the split dose, regardless of whether the second part of the split dose was administered, at any medication session.

Study drug exposure by medication session for participants in the Phase 3 pool is presented in Table 19. Almost all of the participants received the intended doses at each medication session, including administration of the second part of the split dose and escalation of dosing from medication session 1 to medication session 2 and medication session 3.

Table 19: Exposure by Medication Session (Pooled Phase 3; Safety Set)

Medication Session Sequential Number MDMA-AT Dose First Part of the Split Dose + Second Part of the Split Dose	MDMA-AT N = 99 n (%)	Placebo + Therapy N = 95 n (%)
Medication Session 1, n	99	95
0 mg	-	95 (100.0)
+ 0 mg	-	93 (97.9)
80 mg	99 (100.0)	-
+ 40 mg	96 (97.0)	-
Medication Session 2, n	96	87
0 mg	-	87 (91.6)
+ 0 mg	-	86 (90.5)
80 mg	2 (2.0)	-
+ 40 mg	2 (2.0)	-
120 mg	94 (94.9)	-
+ 60 mg	93 (93.9)	-
Medication Session 3, n	95	80
0 mg	-	80 (84.2)
+ 0 mg	-	77 (81.1)
80 mg	3 (3.0)	-
+ 40 mg	3 (3.0)	-
120 mg	92 (92.9)	-
+ 60 mg	91 (91.9)	-

MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; MS: medication session
Percentages are calculated using the total number of participants in each treatment group (N) as the denominator.
Dosing data for 2 MAPP2 participants were incorrect in the database: one participant was actually dosed 100 mg + 40 mg at MS3 instead of 120 mg + 60 mg; 1 was actually dosed 40 mg + 80 mg at MS1 instead of 80 mg + 40 mg.
"+" refers to the dose of the second part of the split dose.
Participants who were dosed at each MS are included.
Source: ISS, Table 14.1.4.4

7.3 Adverse Events

The overall summary of AEs in the Phase 3 pool was generally similar across treatment groups (Table 20).

There were no deaths and no participants in the MDMA-AT group had an SAE. A higher proportion of participants reported TEAEs leading to discontinuation in the placebo group (5.3% [n = 5]) compared to the MDMA-AT group (1.0% [n = 1]). Most of the participants experienced TEAEs within the 2 days of dosing.

Table 20: Overall Summary of Adverse Events (Pooled Phase 3; Safety Set)

Number of Participants	MDMA-AT N = 99 n (%)	Placebo + Therapy N = 95 n (%)
TEAEs	99 (100.0)	93 (97.9)
Severe TEAEs	9 (9.1)	9 (9.5)
TEAEs with first occurrence on Day 0, 1, or 2 relative to medication session	98 (99.0)	85 (89.5)
TEAEs leading to discontinuation of IMP	1 (1.0)	5 (5.3)
Treatment-emergent SAE	0 (0.0)	2 (2.1)
SAEs leading to death	0 (0.0)	0 (0.0)

IMP: investigational medicinal product; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; SAE: serious adverse event; TEAE: treatment-emergent adverse event
TEAEs leading to IMP discontinuation were identified based on the action taken with study treatment of drug withdrawn, or if not available, "discontinued medication session."
Percentages are calculated using the number of participants in each treatment group (N) as the denominator.
Source: ISS, Table 14.3.1.3.1

7.3.1 Common Adverse Events

The most common TEAEs (occurring in the highest proportion of participants who received MDMA-AT) were headache (MDMA-AT: 71.7%; placebo: 57.9%), muscle tightness (MDMA-AT: 59.6%; placebo: 20.0%), decreased appetite (MDMA-AT: 43.4%; placebo: 10.5%), insomnia (MDMA-AT: 39.4%; placebo: 29.5%), suicidal ideation (MDMA-AT: 39.4%; placebo: 44.2%), nausea (MDMA-AT: 38.4%; placebo: 16.8%), and anxiety (MDMA-AT: 30.3%; placebo: 30.5%) (Table 21).

Relatedness to study drug was determined programmatically and defined as TEAEs with a ≥ 2-fold difference in frequency between the MDMA-AT and placebo groups. The most frequently reported related TEAEs were muscle tightness, decreased appetite, and nausea.

Table 21: Most Common (≥5%) Treatment-Emergent Adverse Events (Pooled Phase 3; Safety Set)

Preferred Term (PT)	MDMA-AT (N = 99) n (%)	Placebo + Therapy (N = 95) n (%)
Headache	71 (71.7)	55 (57.9)
Muscle tightness[a]	59 (59.6)	19 (20.0)
Decreased appetite[a]	43 (43.4)	10 (10.5)
Insomnia	39 (39.4)	28 (29.5)
Suicidal ideation	39 (39.4)	42 (44.2)
Nausea[a]	38 (38.4)	16 (16.8)
Anxiety	30 (30.3)	29 (30.5)
Fatigue	28 (28.3)	23 (24.2)
Hyperhidrosis[a]	28 (28.3)	4 (4.2)
Dizziness	24 (24.2)	13 (13.7)

Preferred Term (PT)	MDMA-AT (N = 99) n (%)	Placebo + Therapy (N = 95) n (%)
Feeling cold[a]	20 (20.2)	6 (6.3)
Feeling hot	18 (18.2)	10 (10.5)
Paraesthesia[a]	15 (15.2)	4 (4.2)
Restlessness[a]	15 (15.2)	2 (2.1)
Dry mouth[a]	14 (14.1)	6 (6.3)
Bruxism[a]	13 (13.1)	2 (2.1)
Feeling jittery[a]	13 (13.1)	0 (0.0)
Mydriasis[a]	13 (13.1)	0 (0.0)
Nystagmus[a]	13 (13.1)	1 (1.1)
Vision blurred[a]	12 (12.1)	1 (1.1)
Chest discomfort[a]	11 (11.1)	4 (4.2)
Chills[a]	11 (11.1)	1 (1.1)
Nightmare	11 (11.1)	10 (10.5)
Tremor[a]	11 (11.1)	3 (3.2)
Abdominal pain upper	10 (10.1)	5 (5.3)
Depressed mood	10 (10.1)	10 (10.5)
Abdominal discomfort	9 (9.1)	6 (6.3)
Myalgia[a]	9 (9.1)	4 (4.2)
Nasopharyngitis	9 (9.1)	9 (9.5)
Pain in jaw	9 (9.1)	7 (7.4)
Palpitations	9 (9.1)	7 (7.4)
Arthralgia	8 (8.1)	8 (8.4)
Back pain	8 (8.1)	7 (7.4)
Hypoaesthesia[a]	8 (8.1)	3 (3.2)
Upper respiratory tract infection	8 (8.1)	7 (7.4)
Vomiting[a]	8 (8.1)	2 (2.1)
Blood pressure increased[a]	7 (7.1)	0 (0.0)
Disturbance in attention	7 (7.1)	6 (6.3)
Dizziness postural[a]	7 (7.1)	2 (2.1)
Feeling abnormal[a]	7 (7.1)	3 (3.2)
Feeling of body temperature change[a]	7 (7.1)	1 (1.1)
Asthenia	6 (6.1)	3 (3.2)
Depression	6 (6.1)	5 (5.3)
Intrusive thoughts[a]	6 (6.1)	0 (0.0)
Muscle spasms[a]	6 (6.1)	2 (2.1)
Pollakiuria[a]	6 (6.1)	1 (1.1)
Thirst	6 (6.1)	3 (3.2)
Anger	5 (5.1)	8 (8.4)
Emotional disorder	5 (5.1)	6 (6.3)
Flashback[a]	5 (5.1)	2 (2.1)

Preferred Term (PT)	MDMA-AT (N = 99) n (%)	Placebo + Therapy (N = 95) n (%)
Gait disturbance[a]	5 (5.1)	1 (1.1)
Irritability	5 (5.1)	7 (7.4)
Neck pain	5 (5.1)	11 (11.6)
Nervousness[a]	5 (5.1)	0 (0.0)
Non-cardiac chest pain[a]	5 (5.1)	2 (2.1)
Pain	5 (5.1)	3 (3.2)

MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; PT: preferred term
a. Related TEAEs, defined as those which occurred with a≥2-fold difference in frequency between the MDMA-AT and placebo groups).
A participant with multiple AEs within a PT is counted only once.
Percentages are calculated using the number of participants in each treatment group (N) as the denominator.
Source: ISS, Table 14.3.6.3

7.3.2 Duration of Related Treatment-emergent Adverse Events

Event level data for duration of related TEAEs is presented in Table 22. Related TEAEs are defined as those that occurred at a frequency ≥2-fold difference between the MDMA-AT and placebo groups. Most of the events resolved within 7 days and, with the exception of myalgia, resolved within 2 days. For participants in the MDMA-AT group who experienced myalgia, 4/12 events (33.3%) and 10/12 events (83.3%) resolved within 2 days and 7 days, respectively.

Table 22: Treatment-emergent Related AEs Reported in ≥ 5% of Participants and Time to Resolution by PT (Pooled Phase 3; Safety Set)

Preferred Term (PT)	MDMA-AT (N = 99) n (%)			Placebo + Therapy (N = 95) n (%)		
Time to Resolution	N (Events)	Events Resolved in 2 Days	Events Resolved in 7 Days	N (Events)	Events Resolved in 2 Days	Events Resolved in 7 Days
Muscle tightness	119	99 (83.2)	109 (91.6)	26	21 (80.8)	25 (96.2)
Decreased appetite	73	64 (87.7)	71 (97.3)	16	10 (62.5)	13 (81.3)
Nausea	62	48 (77.4)	52 (83.9)	26	21 (80.8)	22 (84.6)
Hyperhidrosis	50	46 (92.0)	48 (96.0)	5	5 (100.0)	5 (100.0)
Dry mouth	26	21 (80.8)	26 (100.0)	6	6 (100.0)	6 (100.0)
Feeling cold	26	26 (100.0)	26 (100.0)	11	11 (100.0)	11 (100.0)
Paraesthesia	24	19 (79.2)	21 (87.5)	7	6 (85.7)	6 (85.7)
Nystagmus	23	23 (100.0)	23 (100.0)	1	1 (100.0)	1 (100.0)
Tremor	22	19 (86.4)	19 (86.4)	3	3 (100.0)	3 (100.0)
Mydriasis	21	21 (100.0)	21 (100.0)	0	0 (0.0)	0 (0.0)
Restlessness	21	16 (76.2)	17 (81.0)	2	2 (100.0)	2 (100.0)
Bruxism	20	15 (75.0)	19 (95.0)	2	0 (0.0)	1 (50.0)
Feeling jittery	19	16 (84.2)	18 (94.7)	0	0 (0.0)	0 (0.0)
Vision blurred	15	14 (93.3)	14 (93.3)	1	1 (100.0)	1 (100.0)

Preferred Term (PT)	MDMA-AT (N = 99) n (%)			Placebo + Therapy (N = 95) n (%)		
Time to Resolution	N (Events)	Events Resolved in 2 Days	Events Resolved in 7 Days	N (Events)	Events Resolved in 2 Days	Events Resolved in 7 Days
Dizziness postural	14	13 (92.9)	14 (100.0)	2	2 (100.0)	2 (100.0)
Chest discomfort	13	12 (92.3)	12 (92.3)	4	3 (75.0)	4 (100.0)
Chills	13	13 (100.0)	13 (100.0)	1	1 (100.0)	1 (100.0)
Myalgia	12	4 (33.3)	10 (83.3)	5	3 (60.0)	4 (80.0)
Vomiting	11	11 (100.0)	11 (100.0)	3	3 (100.0)	3 (100.0)
Blood pressure increased	10	9 (90.0)	10 (100.0)	0	0 (0.0)	0 (0.0)
Feeling of body temperature change	10	10 (100.0)	10 (100.0)	1	1 (100.0)	1 (100.0)
Flashback	10	6 (60.0)	6 (60.0)	2	1 (50.0)	2 (100.0)
Feeling abnormal	9	7 (77.8)	9 (100.0)	3	2 (66.7)	2 (66.7)
Hypoaesthesia	9	6 (66.7)	6 (66.7)	3	3 (100.0)	3 (100.0)
Gait disturbance	7	7 (100.0)	7 (100.0)	1	1 (100.0)	1 (100.0)
Pollakiuria	7	7 (100.0)	7 (100.0)	2	2 (100.0)	2 (100.0)
Intrusive thoughts	6	1 (16.7)	2 (33.3)	0	0 (0.0)	0 (0.0)
Muscle spasms	6	5 (83.3)	5 (83.3)	3	1 (33.3)	2 (66.7)
Nervousness	6	5 (83.3)	5 (83.3)	0	0 (0.0)	0 (0.0)
Non-cardiac chest pain	6	2 (33.3)	2 (33.3)	2	2 (100.0)	2 (100.0)

AE: adverse event; MDMA-AT: 3,4 methylenedioxymethamphetamine-assisted therapy; TEAE: treatment emergent adverse event
Percentages are calculated using the number of events (N [Events]) for each preferred term as the denominator.
TEAEs with a ≥2-fold difference in frequency between the MDMA-AT and placebo groups are included.
Source: ISS, Table 14.3.4.3

7.3.3 Treatment-emergent Adverse Events by Severity

The majority of reported TEAEs were mild to moderate in severity.

Severe TEAEs in the system organ class (SOC) of psychiatric disorders were reported by a similar number of participants in each group (MDMA-AT: 7.1% [n = 7]; placebo: 7.4% [n = 7]). In the MDMA-AT group, severe TEAEs in the SOC of psychiatric disorders were flashback (2 [2.0%]), anger, emotional distress, obsessive rumination, depression, dissociation, and grief reaction (each reported by 1 participant [1.0%]). In the placebo group severe psychiatric TEAEs by PT were anxiety (2 [2.1%]), insomnia (2 [2.1%]), depression, panic attack, suicide attempt, suicidal ideation, and agitation (each reported by 1 participant [1.1%]).

7.3.4 Treatment-emergent Adverse Events on Day of and 2 Days Following a Medication Session

The overall summary of TEAEs reported on the day of and the 2 days following a medication session across all medication sessions in the Phase 3 pool is presented in Table 23.

Most TEAEs that occurred on the day of and the 2 days following a medication session were mild (MDMA-AT: 53.5%; placebo: 53.7%) or moderate (MDMA-AT: 43.4%; placebo: 33.7%) in severity.

In general, the frequencies of the most common AEs occurring within 2 days of dosing were similar at each medication session (i.e., TEAEs did not occur more frequently at the higher dose sessions [medication session 2 and medication session 3] compared to lower dose session [medication session 1]).

Table 23: Adverse Events That Occurred on the Day of and 2 Days Following a Medication Session in ≥5% of Participants in the MDMA-AT Group (Pooled Phase 3; Safety Set)

System Organ Class (SOC) Preferred Term (PT)	**MDMA-AT (N = 99) n (%)**	**Placebo + Therapy (N = 95) n (%)**
Number of Participants with at least 1 TEAE	98 (99.0)	85 (89.5)
Cardiac disorders	9 (9.1)	4 (4.2)
Palpitations	8 (8.1)	4 (4.2)
Ear and labyrinth disorders	5 (5.1)	3 (3.2)
Eye disorders	31 (31.3)	0 (0.0)
Mydriasis	13 (13.1)	0 (0.0)
Vision blurred	12 (12.1)	0 (0.0)
Gastrointestinal disorders	58 (58.6)	27 (28.4)
Nausea	37 (37.4)	12 (12.6)
Dry mouth	14 (14.1)	6 (6.3)
Abdominal pain upper	10 (10.1)	5 (5.3)
Abdominal discomfort	8 (8.1)	2 (2.1)
Vomiting	7 (7.1)	0 (0.0)
General disorders and administration site conditions	64 (64.6)	34 (35.8)
Fatigue	22 (22.2)	17 (17.9)
Feeling cold	20 (20.2)	6 (6.3)
Feeling hot	18 (18.2)	10 (10.5)
Feeling jittery	12 (12.1)	0 (0.0)
Chest discomfort	11 (11.1)	1 (1.1)
Chills	10 (10.1)	1 (1.1)
Feeling of body temperature change	7 (7.1)	1 (1.1)
Thirst	6 (6.1)	3 (3.2)
Feeling abnormal	5 (5.1)	2 (2.1)
Gait disturbance	5 (5.1)	1 (1.1)
Investigations	9 (9.1)	2 (2.1)

System Organ Class (SOC) Preferred Term (PT)	MDMA-AT (N = 99) n (%)	Placebo + Therapy (N = 95) n (%)
Blood pressure increased	6 (6.1)	0 (0.0)
Metabolism and nutrition disorders	42 (42.4)	8 (8.4)
Decreased appetite	41 (41.4)	8 (8.4)
Musculoskeletal and connective tissue disorders	66 (66.7)	25 (26.3)
Muscle tightness	56 (56.6)	16 (16.8)
Pain in jaw	9 (9.1)	3 (3.2)
Muscle spasms	5 (5.1)	2 (2.1)
Myalgia	5 (5.1)	2 (2.1)
Nervous system disorders	82 (82.8)	57 (60.0)
Headache	66 (66.7)	50 (52.6)
Dizziness	24 (24.2)	13 (13.7)
Paraesthesia	15 (15.2)	4 (4.2)
Nystagmus	13 (13.1)	1 (1.1)
Tremor	11 (11.1)	3 (3.2)
Dizziness postural	7 (7.1)	2 (2.1)
Hypoaesthesia	7 (7.1)	3 (3.2)
Disturbance in attention	6 (6.1)	6 (6.3)
Psychiatric disorders	71 (71.7)	51 (53.7)
Insomnia	29 (29.3)	14 (14.7)
Suicidal ideation	19 (19.2)	20 (21.1)
Anxiety	18 (18.2)	11 (11.6)
Bruxism	12 (12.1)	0 (0.0)
Restlessness	12 (12.1)	2 (2.1)
Nightmare	5 (5.1)	2 (2.1)
Renal and urinary disorders	11 (11.1)	1 (1.1)
Pollakiuria	6 (6.1)	1 (1.1)
Respiratory, thoracic, and mediastinal disorders	14 (14.1)	9 (9.5)
Skin and subcutaneous tissue disorders	32 (32.3)	7 (7.4)
Hyperhidrosis	28 (28.3)	4 (4.2)
Vascular disorders	9 (9.1)	5 (5.3)

AE: adverse event; IMP: investigational medicinal product; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event
A participant with multiple AEs within an SOC or PT is counted only once.
Percentages are calculated using the number of participants in each treatment group (N) as the denominator.
Source: ISS, Table 14.3.2.3.12

7.4 Treatment-emergent Adverse Events Leading to Discontinuation

A total of 6 participants in the pooled Phase 3 studies reported at least 1 TEAE that led to study drug discontinuation (Table 24). In the MDMA group, 1 participant reported a severe TEAE of depression that led to study drug discontinuation. In the placebo group, a total of 5 participants discontinued due to TEAEs: mild suicidal ideation, moderate suicidal ideation, insomnia, and abdominal pain (reported in 1 participant each) and

1 participant who reported 3 TEAEs leading to discontinuation (panic attack and 2 TEAEs of suicide attempt, one moderate and one severe in severity).

Table 24: Adverse Events Leading to Discontinuation (Pooled Phase 3; Safety Set)

Preferred Term, %	MDMA-AT (N = 99) n (%)	Placebo + Therapy (N = 95) n (%)
TEAEs leading to discontinuation	1 (1.0)	5 (5.3)
Depression	1 (1.0)	0 (0.0)
Suicide attempt	0 (0.0)	1 (1.1)
Suicidal ideation	0 (0.0)	2 (2.1)
Severe insomnia	0 (0.0)	1 (1.1)
Abdominal pain	0 (0.0)	1 (1.1)
Panic attack	0 (0.0)	1 (1.1)

AE: adverse event; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; TEAE: treatment-emergent adverse event
Participants could report > 1 TEAE leading to discontinuation.
Source: ISS, Table 14.3.8.3 and Listing 16.2.7.1

7.5 Treatment-emergent Serious Adverse Events

There were no SAEs reported in the MDMA-AT group and 2 participants in the placebo group had at least 1 SAE; 1 (1.1%) participant in the placebo group reported a severe SAE of suicidal ideation 10 days after the last medication session and 1 (1.1%) additional participant in the placebo group reported SAEs of suicide attempt (2 events; 11 and 82 days after last medication session; moderate and severe in severity, respectively) (Table 25).

Table 25: Serious Adverse Events (Pooled Phase 3; Safety Set)

Preferred Term, %	MDMA-AT N = 99	Placebo + Therapy N = 95
SAEs	0 (0.0)	2 (2.1)
Suicidal ideation	0 (0.0)	1 (1.1)
Suicide attempt	0 (0.0)	1 (1.1)

MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; SAE: serious adverse event
Source: ISS, Table 14.3.7.3

SAEs were reported by a total of 12 participants in the pooled studies (10 participants who received MDMA and 2 participants who received placebo) and 8 participants in the non-pooled studies (all 8 participants received MDMA). All SAEs that were reported occurred in 3 or fewer participants. The most common SAEs were suicidal ideation (3 participants [MDMA-AT: 2 participants, placebo: 1 participant]) and suicide attempt (MDMA-AT: 1 participant, placebo: 1 participant).

Of the 2 MDMA-AT participants with SAEs of suicidal ideation, 1 participant received low dose MDMA 30 to 40 mg and the other participant reported this SAE during the long term follow-up (onset of 268 days after last dose). The SAE of suicide attempt in the MDMA-AT group occurred 28 days after the last medication session.

7.6 Deaths

Two participants died in the clinical development program. Both occurred in Phase 2 studies more than 6 months after the completion of dosing. In a study of participants with anxiety related to life-threatening illness (MDA-1), one participant experienced SAEs of chordoma, spinal cord paralysis, cerebrovascular accident, and meningitis and sepsis, which were assessed as the cause of death. The second participant died following completion of study MP-2, a Phase 2 study of patients with treatment-resistant PTSD. The cause of death was relapse of breast cancer with brain metastases. Both events were assessed as not related to study drug.

7.7 Special Safety Topics of Interest Related to MDMA or Participant Population

Special safety topics were identified for detailed evaluation based on the MOA of MDMA, characteristics of the PTSD population, safety issues reported in the published literature (both in non-sponsored clinical trials and with illicit MDMA use), and Phase 2 sponsored clinical trials. The protocols contained risk mitigation measures, including inclusion and exclusion criteria, instructions to identify these potential risks, and measures to mitigate risk and ensure the safety of participants, such as dosage adjustment or treatment withdrawal.

7.7.1 Neuropsychological and Physiological Effects

7.7.1.1 Summary

MDMA may result in temporary alterations in perception, mental state, cognition, and sensation, such as increases in feelings of empathy, openness and social connectedness and decreases in sensitivity to negative emotions such as fear or anger (Borissova et al., 2021; Hysek et al., 2014; Bedi et al. 2010). These acute effects are thought to be important in long-term treatment benefit. This altered mental state may also result in patient impairment, and there is a risk of serious harm resulting from patient impairment. In the clinical development program, there was 1 participant who sustained serious harm of this nature, resulting from significant boundary violations, unethical behavior, and sexual misconduct in the Phase 2 study, MP-4. The event was reported to the Sponsor after the study had concluded and was investigated; there was no evidence of misconduct with other participants at this site.

Of note, subjective experiences in response to MDMA with regard to sensation, perception, mood, and cognition were not collected in the Sponsor's Phase 3 program, unless they had been reported as AEs.

Other known effects of MDMA include perceptual changes such as a heightened and/or altered awareness of sensory input, physical surroundings, and passage of time (Vollenweider et al, 1998; Greer and Tolbert, 1986). These may also include a range of alterations in emotions, thoughts, and physical sensations. Physiological effects observed in the Phase 3 studies included dizziness (24.2% of the MDMA-AT group), gait disturbance (5.1%), blurred vision (12.1%), and nystagmus (13.1%) (Table 21).

7.7.1.2 Risk Mitigation

Risk mitigation strategies are included in the proposed REMS for the product, including specific requirements for the healthcare setting in which it is taken and patient monitoring; the proposed product label which informs the prescriber of this risk and risk mitigation measures that should be taken, including driving restrictions after the medication sessions. Additionally, these measures will be included in QHP (i.e., therapist) education. These measures are described in more detail in Table 28.

7.7.1 Suicidality

Suicidal ideation and behavior occur frequently in patients with PTSD, as described previously (Section 2.1).

7.7.1.1 Summary

In the Phase 3 studies, suicidal ideation and suicidal behavior were assessed by the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a clinician-administered measure of suicide risk which assesses the presence of suicidal ideation, ideation intensity, and suicidal behavior. The C-SSRS was administered at screening (lifetime history of suicidal ideation and behavior), at baseline (prior to the first medication session, since last visit time period), and frequently during the study after dosing, including during both during in-person visits and telephone contacts (since last visit time period).

At screening, in the MDMA-AT and placebo groups, 86.9% and 88.4% of participants had any lifetime history of suicidal ideation (defined as a C-SSRS suicidal ideation score of > 0), and 35.4% and 36.8% participants had lifetime suicidal ideation scores of 4 or 5 (considered serious ideation), respectively. In the MDMA-AT and placebo groups, 27.3% and 30.5% had prior history of suicidal behavior, respectively.

Increases in C-SSRS score after the first dose, compared to the baseline score, were reported as AEs, as were any events of suicidal behavior. The percentages of participants who reported treatment-emergent suicidal ideation were similar in the 2 treatment groups (MDMA-AT: 39.4%; placebo: 44.2%), as were the frequencies of intentional self-injury (MDMA-AT: 3.0%; placebo: 5.3%) (Table 26).

Table 26: TEAEs of Suicidal Ideation, Intentional Self-Injury, Suicidal Behavior, Suicide Attempt, and Self-Injurious Behavior (Phase 3 Pool; Safety Set)

Preferred Term (PT)	MDMA-AT (N = 99) n (%)	Placebo + Therapy (N = 95) n (%)
Suicidal Ideation	39 (39.4)	42 (44.2)
Intentional self-injury	3 (3.0)	5 (5.3)
Suicidal behavior	0 (0.0)	2 (2.1)
Suicide attempt	0 (0.0)	1 (1.1)
Self-injurious ideation	0 (0.0)	1 (1.1)

AE: adverse event; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; PT: preferred term
A TEAE is defined as an AE that occurred after study drug administration.
A participant with multiple AEs within a PT is counted only once.
Percentages are calculated using the number of participants in each treatment group (N) as the denominator.
Source: ISS, Table 14.3.2.3.1

Few participants had treatment-emergent serious suicidal ideation, defined as post-baseline C-SSRS scores of 4 or 5 (MDMA-AT: 4.1%; placebo: 3.2%). One participant in the MDMA-AT group had a worst post-baseline score of 5; this participant had a prior history of suicidal ideation (lifetime score of 5) but no suicidal ideation on the Baseline C-SSRS. Three participants in the placebo group had a worst post-baseline score of 5.

In the MDMA-AT group, the worst post-baseline score was 4 in 3 participants; all 3 participants had a history of suicidal ideation as assessed by the lifetime C-SSRS assessment at Screening. The Baseline C-SSRS scores in these 3 participants were 1, 0, and 3. In the placebo group, 1 participant had a worst post-Baseline score of 4. All 4 participants had prior history of suicidal ideation, as assessed by the Lifetime C-SSRS assessment.

No participants without a prior history of suicidal behavior developed treatment-emergent suicidal behavior post-baseline.

7.7.1.2 Risk Mitigation

In order to mitigate the risk of clinical worsening and emergence of suicidal thoughts and behaviors, this risk will be described in the proposed product label as a warning and precaution (Section 8). Prescribers will be informed about the need to monitor all PTSD patients for clinical worsening and emergence of suicidal thoughts and behaviors especially during concomitant dose changes and after medication sessions. Prescribers will also be informed that improvement does not preclude need for clinically warranted hospitalization. Patients will be monitored post-session for this risk.

In addition, QHP (i.e., therapist) education will include material addressing these risks in this patient population and will outline measures to address any emergent or increased psychiatric symptoms, including suicidality.

7.7.2 Blood Pressure and Heart Rate

MDMA is known to increase heart rate and blood pressure in a dose-dependent manner, based on its sympathomimetic effects (Mas et al, 1999; Harris et al, 2002; Kolbrich et al, 2008b; Kirkpatrick et al, 2014a). In this section, the acute effects of MDMA on BP and HR during the Phase 3 medication sessions are presented. In addition, results from Study MPKF are summarized, in which frequent BP and HR measurements were done up to 72 hours following administration of single doses of MDMA 120 mg to healthy volunteers in the fed or fasted state (Appendix 11.5.1).

7.7.2.1 Phase 3 Studies

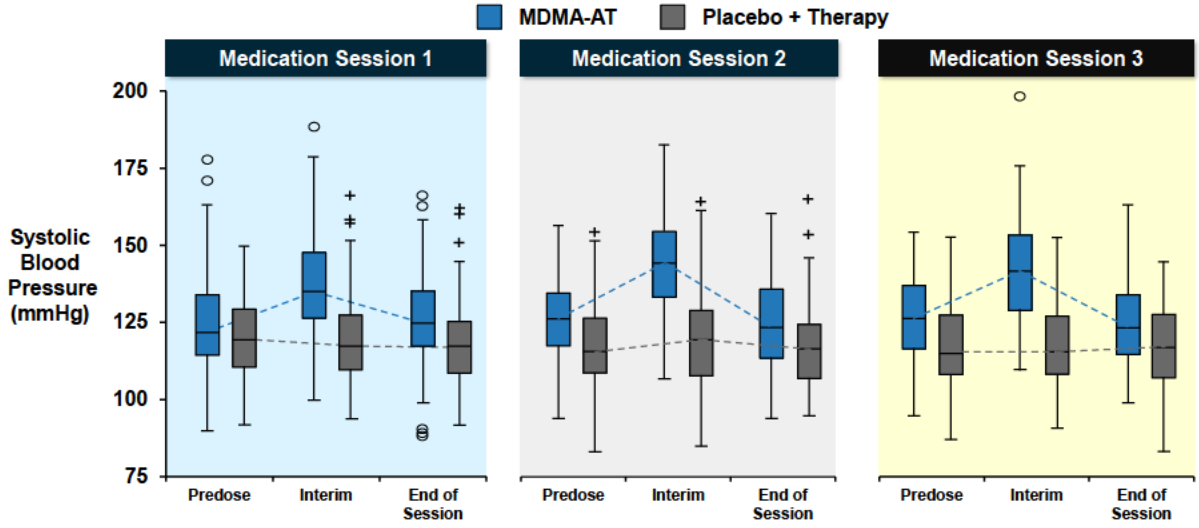
In the Phase 3 studies, in order to mitigate the risk of harm from acute increases in BP and HR, entry criteria, which included CV history, and, in certain participants, the results of additional screening tests, ensured that participants who may be at significant risk (e.g., history of myocardial infarction or cerebrovascular accident) were excluded from the trials. Participants with controlled hypertension were included (Section 6.2.4).

During medication sessions, BP and HR measurements were taken prior to dosing, 1.5-2 hours after the first part of the split dose (prior to administration of the second part of the split dose), and at the end of the medication session. BP was also assessed at the Termination Visit.

7.7.2.1.1 Blood Pressure

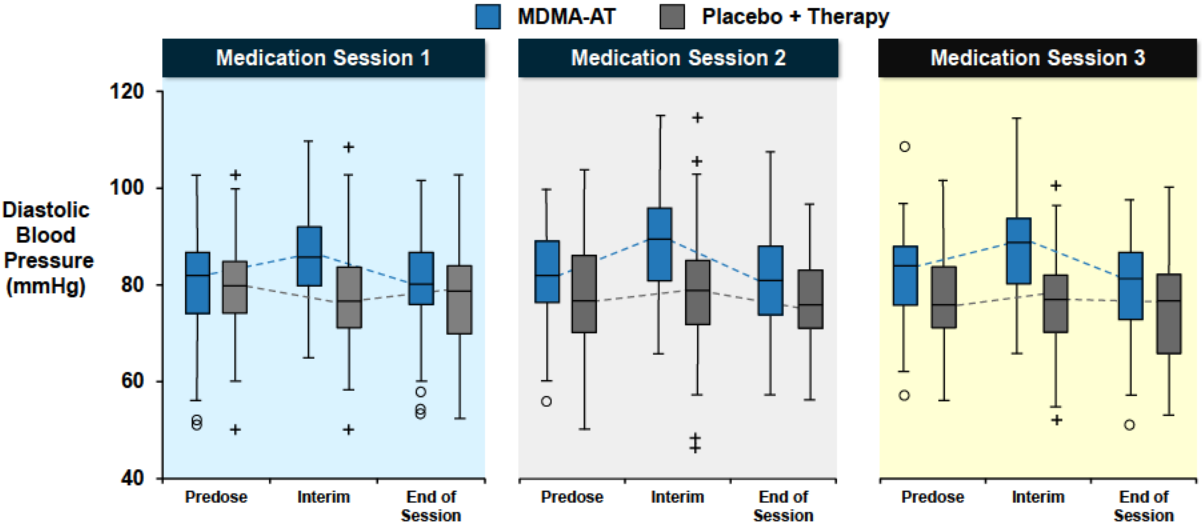
Figure 27, Figure 28, and Figure 29 present the changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the predose, interim, and end-of-session timepoints during each of the 3 medication sessions. Table 33 (Appendix 11.3.8) summarizes the mean observed values and changes from predose measurements at each medication session. As described previously (Table 19), nearly all participants received the intended dosing at each session (80 mg followed by 40 mg at medication session 1 and 120 mg followed by 60 mg at medication sessions 2 and 3). In the MDMA-AT group, increases in mean SBP were greater at medication sessions 2 and 3 (18.2 mmHg and 17.1 mmHg, respectively) than at medication session 1 (12.8 mmHg). Mean increases in DBP were similar across the 3 medication sessions (6.0, 7.0, and 6.0 mmHg, respectively). SBP and DBP generally returned to predose levels by the end-of-session, approximately 5 hours after the second part of the split dose was administered.

Figure 27: Systolic Blood Pressure (Pooled Phase 3)



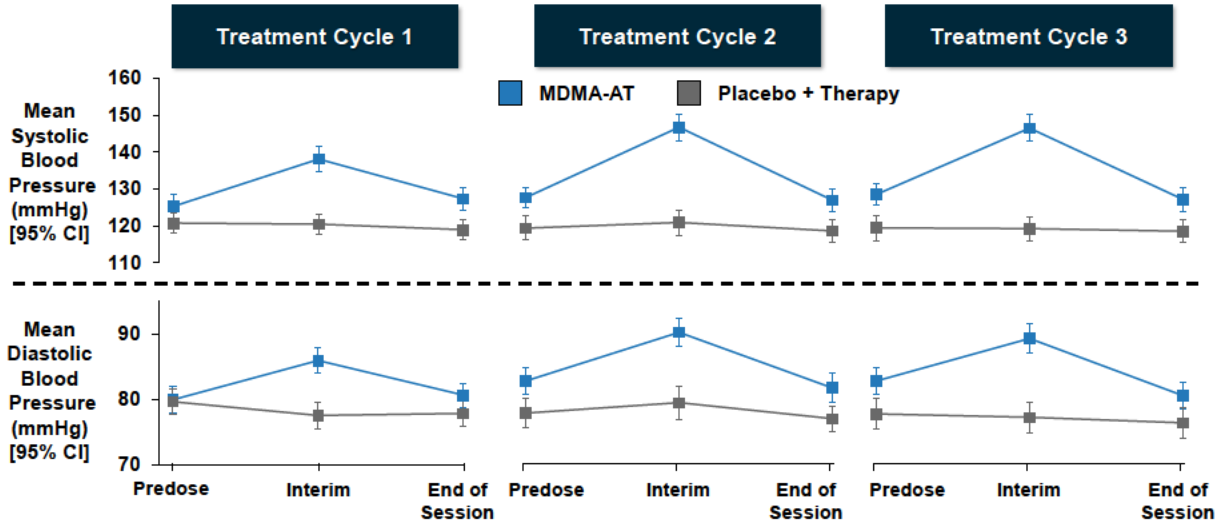
Interim: 1.5 to 2 hours after first part of split dose; end of session: 6.5 to 7 hours after first part of split dose or ~ 5 hours after second part of split dose
Boxes span the interquartile range (25th to 75th percentile), horizontal line = median; whiskers = 1.5x the interquartile range; individual outliers are those that are beyond this range.
Source: Table 14.6.4.2 (ISS Table 81)

Figure 28: Diastolic Blood Pressure (Pooled Phase 3)



Interim: 1.5 to 2 hours after first part of split dose; end of session: 6.5 to 7 hours after first part of split dose or ~ 5 hours after second part of split dose.
Boxes span the interquartile range (25th to 75th percentile), horizontal line = median; whiskers = 1.5x the interquartile range; individual outliers are those that are beyond this range.
Source: Table 14.6.4.2 (ISS Table 81)

Figure 29: Systolic and Diastolic Blood Pressure Over 3 Treatment Cycles



Interim: 1.5 to 2 hours after first part of split dose; end of session: 6.5 to 7 hours after first part of split dose or ~ 5 hours after second part of split dose
Source: Table 14.6.4.2 (ISS Table 81)

Table 27 presents potentially clinically significant high SBP and DBP (and increases from baseline) after drug administration by dose group (based on the first part of the split dose, 80 mg or 120 mg) and, for the 120 mg dose group, by medication session. The 80 mg dose group includes participants who received 80 mg at medication sessions 1, 2, or 3.

In the MDMA 80 mg dose group, maximum SBP ≥ 140 mmHg occurred in 45.5% of participants, with 21.2% experiencing SBP ≥ 140 mmHg and increases from predose ≥ 20 mmHg. More participants who received 120 mg experienced these potentially clinically significant SBPs than those who received 80 mg. The corresponding frequencies in the participants who received 120 mg at medication session 2 were 61.7% and 34.0%, and at medication session 3 the frequencies were 56.5% and 37.0%, respectively. In the placebo group, maximum SBP ≥ 140 mmHg at any medication session occurred in 26.3% of participants; and in 9.5% SBP ≥ 140 mmHg occurred with an increase from the overall baseline (predose medication session 1) ≥ 20 mmHg.

Few participants who received any dose of study drug had SBP ≥ 180 mmHg and no participants who received placebo had a SBP ≥ 180 mmHg. Few participants who received any dose of study drug had DBP ≥ 110 mmHg and 1 participant who received placebo had a DBP ≥ 110 mmHg.

Table 27 does not include potentially clinically significant SBP and DBP at the Termination Visit. One additional participant, who had a history of hypertension, experienced a SBP ≥ 180 and DBP ≥ 110 mmHg at the Termination Visit approximately 2 months after the last medication session.

Table 27: Potentially Clinically Significant High Blood Pressure Results after Drug Administration by Dose Group (Pooled Phase 3; Safety Set)

Parameter Criteria	MDMA-AT 80 mg (N = 99) n (%)	MDMA-AT (N = 95) n (%)		Placebo (N = 95) n (%)
		Session 2	Session 3	Session 1, 2, or 3
Systolic blood pressure (mmHg), N1	99	94	92	95
≥ 140 mmHg	45 (45.5)	58 (61.7)	52 (56.5)	25 (26.3)
≥ 160 mmHg	14 (14.1)	20 (21.3)	20 (21.7)	4 (4.2)
≥ 180 mmHg	2 (2.0)	3 (3.2)	1 (1.1)	0 (0.0)
Increase of ≥ 20 mmHg	32 (32.3)	41 (43.6)	42 (45.7)	16 (16.8)
Increase of ≥ 30 mmHg	14 (14.1)	15 (16.0)	19 (20.7)	6 (6.3)
Increase of ≥ 40 mmHg	3 (3.0)	7 (7.4)	7 (7.6)	1 (1.1)
≥ 140 mmHg and increase of ≥ 20 mmHg	21 (21.2)	32 (34.0)	34 (37.0)	9 (9.5)
Diastolic blood pressure (mmHg), N1	99	94	92	95
≥ 90 mmHg	39 (39.4)	56 (59.6)	51 (55.4)	35 (36.8)
≥ 100 mmHg	12 (12.1)	17 (18.1)	16 (17.4)	10 (10.5)
≥ 110 mmHg	1 (1.0)	3 (3.2)	1 (1.1)	1 (1.1)
Increase of ≥ 10 mmHg	39 (39.4)	41 (43.6)	42 (45.7)	30 (31.6)
Increase of ≥ 20 mmHg	5 (5.1)	10 (10.6)	11 (12.0)	5 (5.3)
Increase of ≥ 25 mmHg	3 (3.0)	2 (2.1)	3 (3.3)	2 (2.1)
≥ 100 mmHg and increase of ≥ 10 mmHg	10 (10.1)	13 (13.8)	13 (14.1)	7 (7.4)
≥ 100 mmHg and increase of ≥ 20 mmHg	3 (3.0)	6 (6.4)	4 (4.3)	2 (2.1)

MDMA: 3,4-methylenedioxymethamphetamine; MS: medication session; N: number of participants; n: number of participants in each category
Dose group is defined as the dose of the first part of the split dose at each experimental session.
Percentages are calculated using the total number of participants who received the first part of the split dose at each experimental session as the denominator. The 120 mg dose was administered as the first part of the split dose at ES2 and ES3. The 80 mg dose was administered as the first part of the split dose at ES1, and, for 2 and 3 participants, respectively, at ES2 and ES3; these participants are included in the 80 mg dose group.
BP categories includes highest BP measurements after predose measurement to the end of session measurement.
Increases in BP for the MDMA-AT group are measured from predose for each experimental session. Increases in BP for the placebo group are measured from overall baseline (predose at ES1).
Source: ISS Table 14.6.1.2.2

AEs of BP increased were reported for 7 participants (5 mild and 2 moderate). All of these participants received the second part of the split dose. No treatments were reported for these AEs.

In MAPP1 and MAPP2 a total of 14 participants had a medical history of hypertension at Baseline. Of these, 1 participant experienced an AE of exacerbated hypertension, which was moderate in severity.

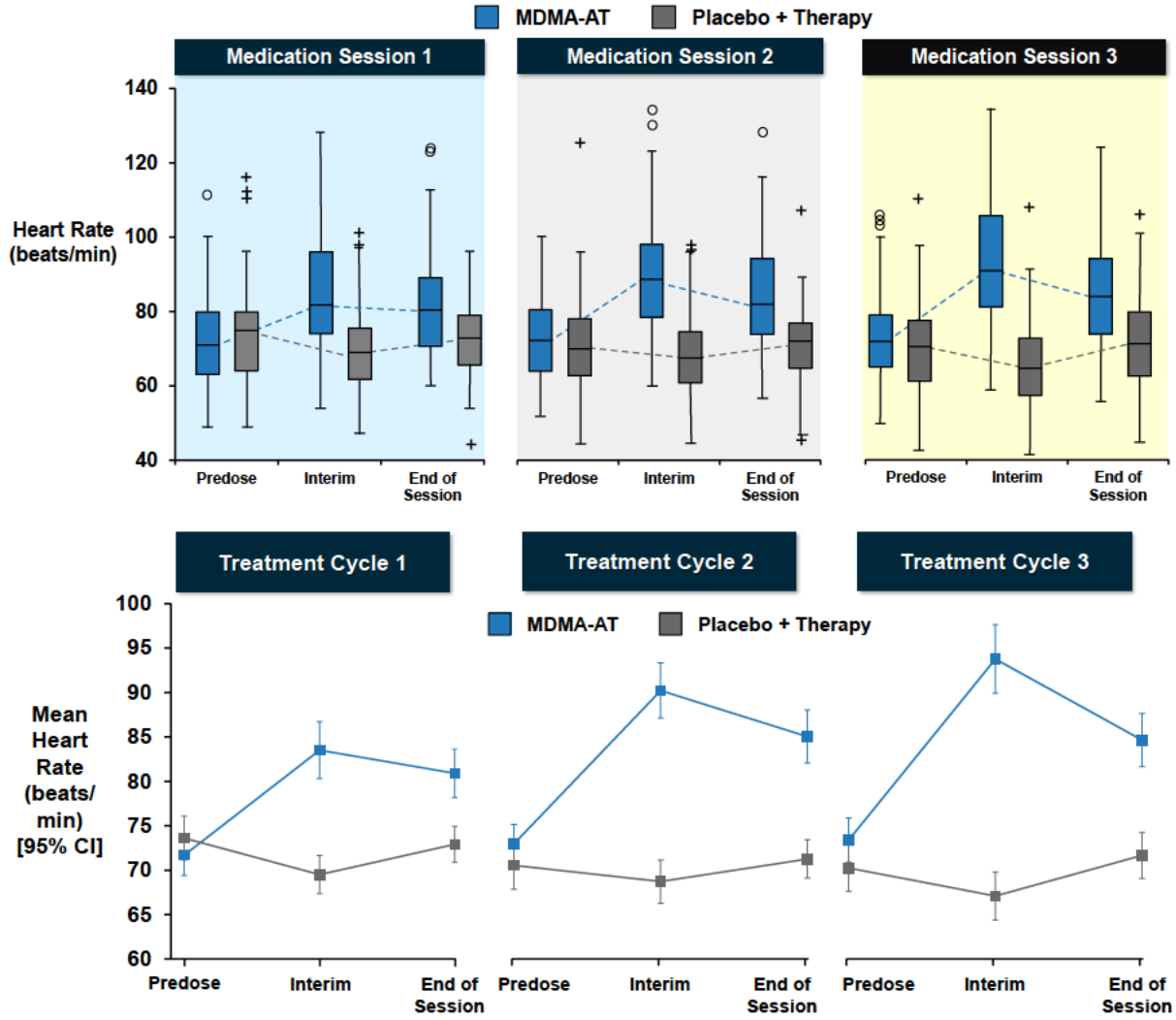
No participants were newly diagnosed with hypertension during the studies.

7.7.2.1.2 Heart Rate

Figure 30 presents the changes in HR at the predose, interim, and end-of-session timepoints during each of the 3 medication sessions. Table 35 (Appendix 11.5.1) summarizes the mean observed values and changes from predose measurements at each medication session. As for SBP, changes in HR at the interim timepoint were greater at medication sessions 2 and 3, at which most participants received the intended first part of the split dose, 120 mg (17.0 bpm and 20.4 bpm, respectively), compared to medication session 1, at which 80 mg was administered (11.8 bpm).

At the end of each session, mean HR remained slightly elevated above predose levels. Mean changes in HR at the end of medication sessions 1, 2, and 3 were 9.2, 11.9, and 11.1 bpm, respectively. However, HR did not remain persistently elevated after the medication sessions, as they returned to the predose levels by the next medication session, 3 to 5 weeks later (Figure 30).

Figure 30: Heart Rate Across All Visits (Phase 3 Pool; Safety Set)



MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy
Interim: 1.5 to 2 hours after first part of split dose; end of session: 6.5 to 7 hours after first part of split dose or ~ 5 hours after second part of split dose
Source: Table 14.6.4.2 (ISS, Table 91)

7.7.2.2 Study MPKF

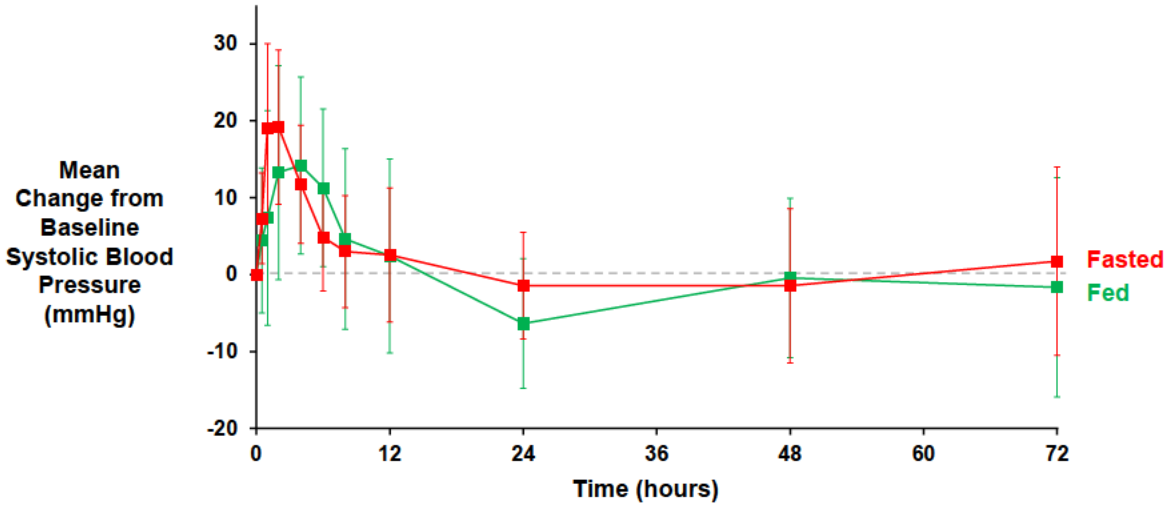
In the Phase 1 food effect study in 16 healthy volunteers, Study MPKF, single doses of 120 mg were administered in the fed and fasted state and frequent BP and HR monitoring was done up to 72 hours after dosing.

7.7.2.2.1 Blood Pressure

Figure 31 and Figure 32 present the time course of mean changes in SBP and DBP following dosing in the fasted and fed states. Table 35 (Appendix 11.5.1) summarizes the mean observed values and changes from predose measurements at each medication session. In the fed group, the peak mean change in SBP from predose

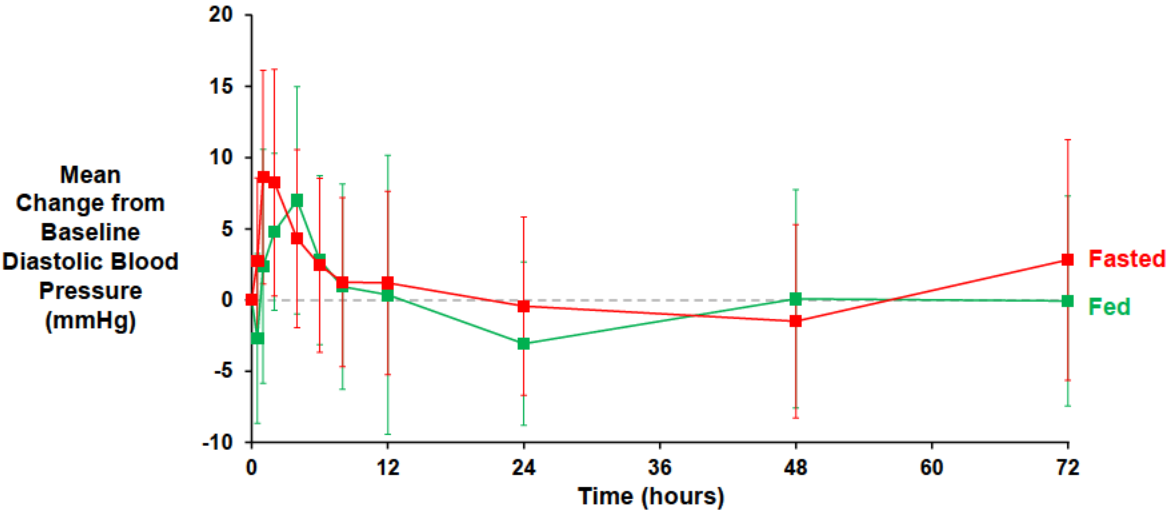
occurred at 4 hours (14.2 mmHg) and, in the fasted group, at 2 hours (19.2 mmHg). The peak mean change in DBP also occurred at 4 hours in the fed group (7.0 mmHg) and occurred at 1 hour in the fasted group (8.6 mmHg). SBP remained slightly elevated at 12 hours in both the fed and fasted groups (increases of approximately 2.5 mmHg from predose) and were at predose levels by 24 hours (Table 35).

Figure 31: Mean (±SD) Change from Baseline to SBP Over Time (MPKF; Safety Analysis Set)



Source: MPKF CSR, Figure 14.3.6.3 and Listing 16.2.8.2

Figure 32: Mean (±SD) Change from Baseline to DBP Over Time (MPKF; Safety Analysis Set)

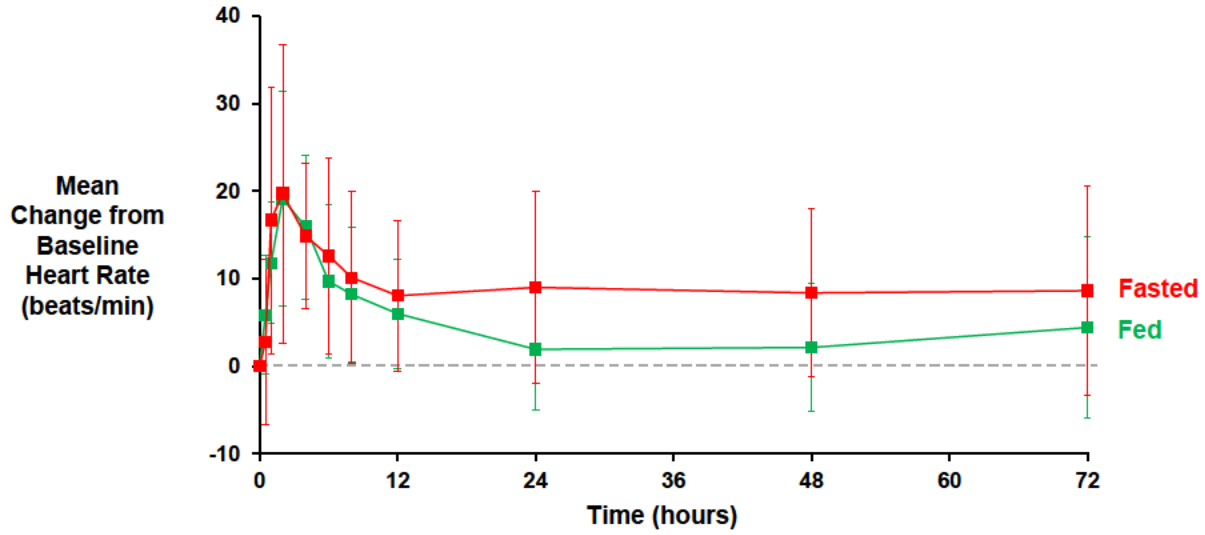


Source: MPKF CSR, Figure 14.3.6.4 and Listing 16.2.8.2

7.7.2.2.2 Heart Rate

Figure 33 presents the time course of mean changes in HR following dosing in the fasted and fed states. Table 36 (Appendix 11.5.1) summarizes the mean observed values and changes from predose measurements at each medication session. In both the fed and fasted groups, the peak mean change in HR occurred at 2 hours (19.1 bpm and 19.8 bpm, respectively). HR decreased but remained elevated at 24 hours (1.9 bpm and 9.0 bpm, respectively, Table 36), which persisted until the 72-hour timepoint (Figure 33).

Figure 33: Mean (±SD) Change from Baseline in HR Over Time (MPKF; Safety Analysis Set)



Source: MPKF CSR, Figure 14.3.6.2 and Listing 16.2.8.2

7.7.2.3 Risk Mitigation

In order to mitigate the risk of adverse outcomes resulting from increases in blood pressure and heart rate, this risk will be described in the proposed product label as a warning and precaution (Section 8). Prescribers will be informed about the need to perform a careful evaluation of the patient's CV status, including additional evaluations, if appropriate, and exercise caution in treating patients who may be at risk of harm from acute increases in blood pressure and heart rate.

7.7.3 Proarrhythmic Potential

The Sponsor implemented a totality of evidence approach to the evaluation of the proarrhythmic potential of MDMA, including nonclinical and clinical studies, which were supported by the published literature.

This evaluation suggests that MDMA has low to no potential impact on QT/QTc interval prolongation and low to no proarrhythmic potential.

7.7.3.1 Summary

The results of in vitro (hERG) and in vivo (dog cardiovascular) studies did not demonstrate the potential for QTc prolongation. The clinical data supporting this conclusion include ECGs collected in the food effect study in healthy volunteers (MPKF), the AEs reported in the Phase 2 and Phase 3 clinical studies, and a review of the published literature. A Thorough QT study was not done as the potential effects of MDMA on QT prolongation would likely be uninterpretable, given the large increases in HR observed following administration.

Electrocardiograms were collected in Study MPKF, the Phase 1 cross-over study in which healthy volunteers were administered single doses of MDMA 120 mg in fed and fasted conditions. No participants developed QT prolongation or experienced TEAEs suggestive of ventricular arrhythmias.

In this study, the concentration/effect relationship of MDMA concentrations on Fridericia QT correction formula (QTcF) was evaluated. A linear mixed-effect model of changes in QTcF interval describes the relationship with a slope of 0.0136 msec and an intercept of -12.5833 msec. The 90% CI for the slope is -0.0119, 0.0390 msec and crosses 0. At the upper bound of the 95% CI for C_{max} the model-predicted CFB in QTcF was -2.6898 msec and -0.4276 msec, respectively. The observation that the 90% CI for the slope of the linear regression line includes 0 and the small negative change in Baseline for QTcF at the upper bound of C_{max} suggest that MDMA did not affect QTcF in this study.

Across all Sponsor studies, only 1 participant experienced a ventricular arrhythmic TEAE, in a Phase 2 study, following a dose of MDMA 125 mg. A rhythm strip showed normal sinus rhythm with unifocal PVCs and runs of trigeminy and quadrigeminy. The screening ECG had showed a single PVC and the event was assessed as exacerbation of pre-existing ectopy, and probably related to MDMA. Subsequently symptoms of chest discomfort and mild shortness of breath were reported. The second part of the split dose was not administered, and the participant was hospitalized for observation and treatment. PVCs decreased in frequency after treatment with metoprolol. There was no evidence of QT prolongation or cardiac ischemia.

With the exception of this participant, no AEs indicative of a proarrhythmic potential of MDMA were reported in the Phase 2 and Phase 3 studies. It should be noted that ECGs were not collected post-dosing in the Phase 2 or Phase 3 studies.

7.7.3.2 Risk Mitigation

Overall, MPKF electrophysiological and clinical data suggest low to no potential impact of MDMA on QT/QTc and low to no proarrhythmic potential. Proarrhythmia represents a potential risk and the proposed product label recommends a cardiovascular evaluation prior to initiation of treatment, similar to recommendations for the assessment of risk of blood pressure and heart rate increases.

7.7.4 Nonmedical Use

7.7.4.1 Summary

The Sponsor conducted an assessment of nonmedical use potential (i.e., an "Abuse Potential Assessment") evaluating numerous sources of data, including a bibliography and analysis of published nonclinical and clinical data, data from the Sponsor's clinical trials, and epidemiological data on illicit MDMA from numerous sources. Illicit MDMA is a known drug of nonmedical use, and data from non-sponsored studies, as well as the published literature, further characterize the potential for nonmedical use of MDMA.

Human studies evaluating the potential for nonmedical use (i.e., "Human Abuse Potential Studies") consistently demonstrate that MDMA produces significant subjective effects in comparison to placebo, with users reporting increased desired effects such as increased positive mood, empathy, and altered perception. There was no direct assessment of the prosocial or other subjective effects related to potential for nonmedical use of MDMA in the Phase 3 program.

Data drawn from sponsor-supported studies suggests that MDMA as a pharmaceutical product has a low potential for nonmedical use when given in the context of a psychological intervention, and when access to the drug is limited to a single session at a time. During the clinical development program, the Sponsor did not collect desired, i.e., positive effects as "abuse"-related AEs.

AEs indicative of "abuse" of MDMA were pre-agreed with the FDA as AEs of special interest (AESI) subject to expedited reporting (Medical Dictionary for Regulatory Affairs (MedDRA) PT: behavioral addiction, drug abuser, substance abuser, dependence, intentional product misuse, overdose, accidental overdose, intentional overdose, prescribed overdose, drug diversion). None of these AEs were reported in the Sponsor's development program.

Furthermore, when used in accordance with the proposed labeling, MDMA is unlikely to create severe psychological and/or physical dependence (as the proposed dose regimen is for acute treatment, development of MDMA dependence is not expected when used as intended).

7.7.4.2 Risk Mitigation

As illicit use of material represented as MDMA is common, the Sponsor has proposed several measures to limit the potential for nonmedical use of MDMA (Section 8.1). The primary measure to limit the nonmedical use potential of the Sponsor's pharmaceutical product is the use of single dose packaging.

Additional controls include a warning and precaution (Section 8) with text indicating that prescribers should assess risk for nonmedical use prior to prescribing and monitor the development of related behaviors or conditions, as well as planned prescriber/QHP (i.e., therapist) and patient education.

7.7.5 Osmoregulatory Effects

MDMA has been reported to be associated with hyponatremia due to inappropriate secretion of antidiuretic hormone arginine (Fallon et al, 2002). MDMA administered as a single dose in a healthcare setting is not expected to have any risks of osmoregulatory changes.

In the Phase 3 pool, in general more participants who received MDMA-AT than placebo reported AEs which may be associated with osmoregulatory effects (hyperhidrosis [MDMA-AT: 28.3%; placebo: 4.2%], thirst [MDMA-AT: 6.1%; placebo: 3.2%], and cold sweat [MDMA-AT: 3.0%; placebo 2.1%]). All events were self-limiting and resolved without medical intervention. It should be noted that no post-dose laboratory testing was done in the Phase 3 studies.

7.7.6 Thermoregulatory Effects

Although hyperthermia has been observed with illicit MDMA, when administered in a clinical setting MDMA produces only a slight increase in body temperature (Liechti et al, 2001). Ambient temperature does not enhance or attenuate this slight elevation in humans. In the Phase 3 studies, no clinically meaningful changes from predose temperature measurements occurred in either the MDMA-AT or placebo groups during the medication sessions.

More participants who received MDMA-AT than placebo reported TEAEs associated with thermoregulation (feeling cold [MDMA-AT: 20.2%; placebo: 6.3%], feeling hot [MDMA-AT: 18.2%; placebo: 10.5%], chills [MDMA-AT: 11.1%; placebo: 1.1%], feeling of body temperature change [MDMA-AT: 7.1%; placebo: 1.1%], temperature intolerance [MDMA-AT: 4.0%; placebo: 2.1%], and hyperthermia [MDMA-AT: 1.0%; placebo: 0]).

7.7.7 Hepatotoxicity

The majority of the Sponsor's trials did not capture clinical laboratory data pertinent to the evaluation of treatment-emergent liver abnormalities, therefore a cumulative review of all available hepatotoxicity data from the published literature was conducted to assess if MDMA is associated with drug-induced liver injury (DILI).

There have been no cases meeting Hy's law laboratory criteria reported in the 217 evaluable participants in clinical trials (sponsored [n = 53]; non-sponsored [n = 164; Vizeli and Liechti, 2017]). As there was no evidence of DILI, no monitoring (symptom or serum testing) or other risk mitigation measures are recommended in the proposed labeling.

7.8 Safety Conclusions

The safety of MDMA has been characterized by the results of 17 clinical studies in which 427 participants were exposed to MDMA, including 287 participants with PTSD and 140 healthy volunteers. Pooled analyses were done on 6 Phase 2 and Phase 3 studies in which 226 participants with at least moderate PTSD were treated with MDMA-AT. These 6 studies include 2 adequate and well-controlled, double-blind,

placebo-controlled studies in which 99 participants were treated with MDMA-AT and 95 participants were treated with placebo. Additional support, particularly for the assessment of key identified and potential risks is provided by the extensive published literature on MDMA administered in non-sponsored clinical trials, as well as relevant epidemiologic data. The results of the clinical studies demonstrate that MDMA was well tolerated.

In the Phase 3 placebo-controlled studies, the most frequent TEAEs (i.e., occurring at a frequency greater than 2-fold compared to the placebo group) were consistent with MDMA's MOA, including dizziness, muscle tightness, bruxism, feeling jittery, perceptual changes in temperature (feeling hot, feeling cold), hyperhidrosis, and visual changes (mydriasis, nystagmus, and blurred vision). Other common treatment-related TEAEs included decreased appetite and nausea. Most TEAEs were mild to moderate in severity and resolved in 2 days of dosing. There were few reported discontinuations due to TEAEs and SAEs, including deaths.

Key risks of MDMA include those that have been identified in the clinical studies and/or the published literature and potential risks due to MDMA's mechanism of action and comorbidities associated with PTSD. These include increases in blood pressure and heart rate, potential proarrhythmic effects, neuropsychological and physiological effects, psychiatric symptoms including suicidal ideation and behavior, and nonmedical use.

Dose-related increases in blood pressure and heart rate, due to sympathomimetic effects of MDMA, occurred in most participants, including potentially clinically significant increases. These effects generally resolved by the end of the medication sessions. No antihypertensive or other treatments or discontinuations/dose reductions of MDMA, or adverse cardiovascular outcomes were reported due to these effects. Although the totality of evidence from the clinical and nonclinical program suggests that there is a low potential for proarrhythmia, this remains a potential risk due to the mechanism of action.

Treatment benefit in PTSD is likely due to the subjective and prosocial effects; however, temporary alterations in mental state (such as reduction of inhibition and mental impairment) may place patients at risk of harm. While evidence of harm was rarely observed in the clinical program, this remains a key neuropsychological risk. Suicidal ideation and behavior occur frequently in patients with PTSD. Although treatment-related suicidality was not observed in the clinical program, this is an expected key risk in patients treated with MDMA-AT. Additionally, acute neurophysiologic effects which were common treatment-related adverse events, described above, may result in patient impairment.

While illicit MDMA is a known drug of nonmedical use, MDMA as a pharmaceutical product has low potential for nonmedical use when taken in accordance with the proposed product label.

The Sponsor has proposed extensive risk mitigation measures to address these key risks, detailed in Section 8, which include appropriate language and instructions for use in the product label, a REMS, and QHP (i.e., therapist) education.

In conclusion, the clinical development program, which include the safety results of 2 double-blind, placebo-controlled Phase 3 studies have adequately characterized the safety profile of MDMA-AT in a representative population of patients with moderate to severe PTSD. Key identified and potential risks can be appropriately managed and mitigated by the proposed risk mitigation measures under discussion with FDA.

8 POST-MARKETING RISK MANAGEMENT AND PHARMACOVIGILANCE

MDMA-AT was generally safe and well-tolerated in the Sponsor's development program. The Sponsor has proposed mitigation strategies for the identified risks of MDMA-AT, both observed and theoretical (Section 7.7), in Table 28. These planned strategies have been integrated into a safe-use framework currently under development by the Sponsor in consultation with FDA (Section 8.2). Stakeholders in this paradigm include prescribers, QHPs (i.e., therapists), and patients. This framework is intended to ensure adequate systems are established to manage identified and emergent risks associated with MDMA-AT in the post-marketing setting.

8.1 Identified Risk Mitigation Strategies

The risks of MDMA-AT identified during development, along with their proposed mitigation strategies are outlined in Table 28.

Table 28: Post-marketing Risk Monitoring and Mitigation

Risk	Context	Proposed Mitigation
Neuropsychological and Physiological Effects/ Patient Impairment	Physiological effects were among the most common MDMA-related AEs observed in the clinical studies. Temporary alterations in mental states may also occur during treatment in the medication sessions and may result in patient impairment/ increased patient vulnerability.	**REMS** to mitigate of the risks of serious harm resulting from patient impairment will ensure that MDMA is taken in certain healthcare settings only after safe-use conditions have been established and that patient monitoring is ongoing during and after the medication session. **Proposed product label** recommends that QHPs providing psychological intervention should have sufficient expertise to anticipate and support patients experiencing these effects. In addition, the product label recommends that patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, should refrain from driving until the day following the medication session, that they may need assistance when standing or walking during the sessions, and that they should pause to sit before standing if they have been lying down during the medication session. **Prescriber/QHP Education** will inform on the heightened risk of impairment and provide tools for ensuring safe-use conditions are upheld and boundaries are maintained while the patient is impaired.
Psychiatric Symptoms/ Suicidality	Theoretical risk due to underlying disease and common comorbidities.	**Proposed product label** recommends that treatment should be halted due to emergence of serious or severe psychiatric symptoms until symptoms have resolved or stabilized and urges caution when treating patients with psychosis or bipolar disorders. Also recommends monitoring of all PTSD patients for clinical worsening and emergence of suicidal thoughts and behaviors especially during concomitant dose changes and after medication sessions and notes that improvement does not preclude need for clinically warranted hospitalization. **REMS** will ensure patients are monitored post-session for this risk. **Prescriber/QHP Education** will include material addressing these risks in this patient population and will outline measures to address any emergent or increased psychiatric symptoms, including suicidality.

Risk	Context	Proposed Mitigation
Blood Pressure and Heart Rate Increases	Dose-dependent increases in BP and HR were identified in clinical trials (consistent with known sympathomimetic effects).	**Proposed product label** recommends that the CV status of patients being considered for treatment should be evaluated by conducting a careful history and physical exam to assess for the presence of cardiac disease with further cardiac evaluation when warranted by the prescribing physician. Additionally, prescribers should exercise caution when treating patients at higher risk of major adverse CV events, particularly patients with known CV and cerebrovascular disease, preexisting hypertension, and patients with advanced age.
Proarrhythmic Potential	Theoretical risk, especially ischemic arrhythmias, due to sympathomimetic effects.	**Proposed product label** recommends an evaluation for the potential for arrhythmias prior to initiation of treatment.
Nonmedical Use/ Substitution	MDMA is a known drug of nonmedical use.	**Product** will be provided in single dose packaging. **Proposed product label** recommends assessing risk for nonmedical use prior to prescribing and monitoring for the development of related behaviors or conditions, using careful consideration prior to treatment of individuals with substance use disorder and only treating if the benefit outweighs the risk of treatment. **Prescriber/QHP Education** will outline the potential dangers of substitution with illicit MDMA. **Patient Education** will remind patient to take MDMA only in certain healthcare settings and will outline the potential dangers of substitution with illicit MDMA
Serotonin Syndrome	Serotonin syndrome is class effect due to the MOA of MDMA, especially when used with concomitant serotonergic drugs and drugs that impair the metabolism of serotonin.	**Proposed product label** recommends class labeling on monitoring for the emergence of serotonin syndrome.

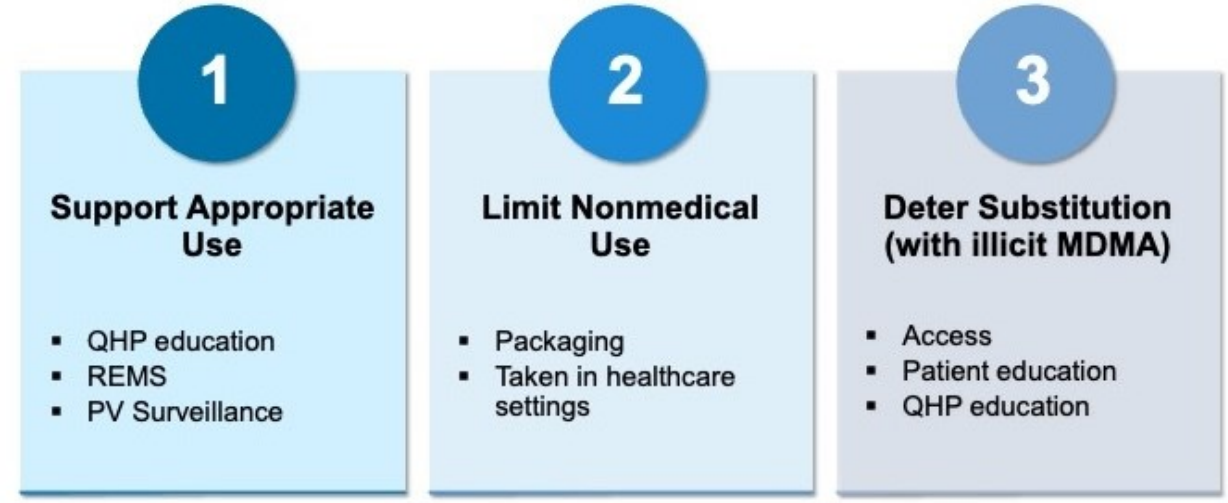
CV: cardiovascular; QHP: qualified healthcare provider; MOA: mechanism of action
Source : Summary of Clinical Safety, Table 29

8.2 Safe Use Framework for MDMA-AT

The Sponsor's goal is to advance the treatment of PTSD through the deliberate, controlled, and high-quality commercialization of MDMA-AT that balances the need for access with the need to establish a safe use framework for MDMA-AT. This expedited development program was intended to support an acute dosing regimen. The Sponsor

intends to study the safety and efficacy of additional medication sessions in the post-marketing setting.

Figure 34: Safe Use Framework for MDMA-AT



8.2.1 MDMA Risk Evaluation and Mitigation Strategy

The Sponsor is engaged with the FDA to develop a REMS program to evaluate and mitigate the risk of serious harm resulting from patient impairment associated with MDMA use. Important requirements of the proposed REMS include the following:

- MDMA must be:
  - Dispensed or taken only in certain health care settings.
  - Dispensed or taken only once evidence of safe-use conditions has been established.
- Patients must be:
  - Monitored during and after treatment (intra and post-session monitoring).
  - Assessed to be stable for discharge.
  - Enrolled in a patient registry.

The details of the REMS program are still under development and the Sponsor will ensure alignment with the FDA on this and any other key areas of concern.

8.2.2 Post-marketing Safety Surveillance

The Sponsor will establish a post-marketing surveillance and risk assessment program to reduce patient risk by monitoring safe product use and identifying safety concerns in adherence to all applicable legislation and guidelines. Under the current proposed REMS, patients will be enrolled in a registry and monitored during and after treatment for specific risks. The Sponsor will engage with the FDA to determine whether any enhanced surveillance or reporting is required to ensure adequate risk management in the post-marketing environment.

8.2.3 QHP Education

The Sponsor plans to offer a MDMA-AT Training Program (Therapy Training Program) to teach QHPs (i.e., therapists) how the treatment was studied in the clinical trials, including the specific psychological intervention that was employed. The program will cover the fundamentals of the MDMA-AT treatment paradigm and convey core educational messages for the appropriate prescribing of MDMA and the administration of psychological intervention. The design and content of the program are informed by the approach used to train QHPs who worked on the pivotal clinical studies, as well as general best practices in training in psychotherapy.

Initially, the Sponsor plans to work with a limited number of sites of care that take specific steps to put the infrastructure, staff, and processes in place that are needed for high-quality delivery of MDMA-AT based on the core educational messages developed from the experience gained from the clinical trial program. In order to support fidelity to the therapeutic approach used in clinical trials, QHPs from these sites of care will be required to enroll in the Sponsor's Therapy Training Program before being permitted to deliver MDMA-AT.

Over time, the Sponsor plans to engage with professional societies or other qualified bodies with the expertise and mandate to develop standards for training in MDMA-AT.

Core educational content will cover:

- Anticipate and support patients experiencing physiological effects that include perceptual changes and temporary alterations in mental states, facilitating intense emotions or increasing vulnerability.
- Establishing and maintaining safe use conditions during the medication sessions.
- Ensuring that patients do not leave the medication session while still experiencing the effects of MDMA.
- Assessing patients for residual emotional distress and exercising clinical judgement to determine whether participants need additional support before ending the session.

8.2.4 Packaging and Compliant Distribution

In order to limit nonmedical use, the product will be provided in single dose packaging. In addition, the product is intended to be taken only in certain healthcare settings as part of a specific therapeutic program.

Additional controls pertaining to distribution and labeling will be required dependent on the DEA rescheduling decision.

9 BENEFIT-RISK CONCLUSIONS

PTSD is an undertreated, serious condition that may be life-threatening. There is a substantial unmet medical need for an additional effective treatment with a positive benefit-risk profile for PTSD. The Sponsor's development program was informed by an extensive body of literature and evaluated the safety and efficacy of an acute regimen of MDMA-AT for the treatment for PTSD.

Evidence of efficacy for MDMA-AT includes 2 positive adequate and well-controlled Phase 3 studies. Treatment with MDMA-AT resulted in statistically significant and clinically meaningful improvements in PTSD symptom severity with additional statistically significant, supportive evidence of clinically meaningful improvement in functional impairment due to PTSD.

MDMA-AT was generally safe and well-tolerated in the Sponsor's development program. The Sponsor is working with the FDA to establish a safe use framework to manage the identified risks, both observed and theoretical. Mitigation strategies include a REMS program with a patient registry, warnings and precautions and recommendations for the prescribing physician in the label, post-marketing surveillance and risk assessment, QHP education (MDMA-AT Training Program), single dose packaging, and DEA-compliant distribution.

MDMA-AT has the potential to provide a substantial treatment benefit to patients who suffer from PTSD. The identified and potential risks can be mitigated by the measures described above. Overall, these data demonstrate that the benefits exceed the risks of MDMA-AT for patients with PTSD. If approved, MDMA-AT will provide patients suffering from PTSD a novel treatment paradigm that engages them in a psychological intervention while offering the benefits of an acute pharmacological intervention. There remains an unmet medical need for effective and well-tolerated treatments for PTSD, a condition representing a wide-spread and serious risk to public health.

10 REFERENCES

Abraham TT, et al. Urinary MDMA, MDA, HMMA, and HMA excretion following controlled MDMA administration to humans. J Anal Toxicol. 2009;33(8):439-446.

Ahmadi N, Hajsadeghi F, Mirshkarlo HB, Budoff M, Yehuda R, Ebrahimi R. Post-traumatic stress disorder, coronary atherosclerosis, and mortality. Am J Cardiol. 2011;108(1):29-33.

Alderman J, Preskorn SH, Greenblatt DJ, Harrison W, Penenberg D, Allison J, Chung M. Desipramine pharmacokinetics when coadministered with paroxetine or sertraline in extensive metabolizers. J Clin Psychopharmacol. 1997 Aug;17(4):284-91. doi: 10.1097/00004714-199708000-00008. PMID: 9241008.

APA. Guideline Development Panel for the Treatment of PTSD in Adults. Clinical practice guideline for the treatment of post-traumatic stress disorder (PTSD) in adults. 2019. https://www.apa.org/ptsd-guideline/ptsd.pdf.

Apotex Inc. Paxil [prescribing information]. Toronto, Ontario: Apotex Inc.; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020031s082,020710s050lbl.pdf.

Barbano AC, et al. Differentiating PTSD from anxiety and depression: lessons from the ICD-11 PTSD diagnostic criteria. Depress. Anxiety. 2019;36(1):490-498.

Bedi GG, Cecchi GA, Slezak DF, et al. A window into the intoxicated mind? Speech as an index of psychoactive drug effects. Neuropsychopharmacology. 2014;39(10): 2340-2348.

Berber MJ. FINISH: remembering the discontinuation syndrome. Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (anxiety/agitation). J Clin Psychiatry. 1998 May;59(5):255.

Berger W, et al. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Mar 17;33(2):169-180.

Borissova A, Ferguson B, Wall MB, Morgan CJ, Carhart-Harris RL, Bolstridge M, Bloomfield MA, Williams TM, Feilding A, Murphy K, Tyacke RJ. Acute effects of MDMA on trust, cooperative behaviour and empathy: A double-blind, placebo-controlled experiment. Journal of Psychopharmacology. 2021 May;35(5):547-55.

Bradley R, Greene J, Russ E, Dutra L, Westen D. A multidimensional meta-analysis of psychotherapy for PTSD. Am J Psychiatry. 2005;162(2):214-227.

Brady K, et al. Efficacy and safety of sertraline treatment of post-traumatic stress disorder: a randomized controlled trial. JAMA. 2000;283(14):1837-1844.

Cami J, et al. Human pharmacology of 3,4 methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol, 2000; 20(4):455-466.

Carhart-Harris RL, Murphy K, Leech R, et al. The Effects of Acutely Administered 3,4-Methylenedioxymethamphetamine on Spontaneous Brain Function in Healthy Volunteers Measured with Arterial Spin Labeling and Blood Oxygen Level-Dependent Resting State Functional Connectivity. Biol Psychiatry. 2015;78(8): 554-562.

Carlson RG, et al. Drug use practices among MDMA/ecstasy users in Ohio: a latent class analysis. Drug Alcohol Depend, 2005. 79(2): p. 167-179.

Cipriani A, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Focus (Am Psychiatr Publ). 2018 Oct;16(4):420-429.

Clemens KJ, Van Nieuwenhuyzen PS, Li KM, Cornish JL, Hunt GE, McGregor IS. MDMA ("ecstasy"), methamphetamine and their combination: long-term changes in social interaction and neurochemistry in the rat. Psychopharmacology (Berl). 2004 May;173(3-4):318-325.

Cole JC, Sumnall HR. Altered states: the clinical effects of Ecstasy. Pharmacol Ther, 2003. 98(1): p. 35-58.

Colvonen PJ, Straus LD, Stepnowsky C, McCarthy MJ, Goldstein LA, Norman SB. Recent Advancements in Treating Sleep Disorders in Co-Occurring PTSD. Curr Psychiatry Rep. 2018 Jun 21;20(7):48.

Crewe HK, Lennard MS, Tucker GT, Woods FR, Haddock RE. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. Br J Clin Pharmacol. 1992 Sep;34(3):262-5. doi: 10.1111/j.1365-2125.1992.tb04134.x. PMID: 1389951; PMCID: PMC1381398.

Davis LL, et al. The Economic Burden of Posttraumatic Stress Disorder in the United States from a Societal Perspective. J Clin Psychiatry. 2022 Apr 25;83(3):21m14116.

De Jong JT, Komproe IH, Van Ommeren M. Common mental disorders in postconflict settings. Lancet. 2003;361(9375):2128-2130.

De la Torre R, et al. Non-linear pharmacokinetics of MDMA (‘ecstasy’) in humans. Br J Clin Pharmacol. 2000;49(2):104-109.

De la Torre R, et al. Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. Therapeutic drug monitoring. 2004;26(2):137-144.

Dorrington S, et al. Trauma, post-traumatic stress disorder and psychiatric disorders in a middle-income setting: prevalence and comorbidity. Br J Psychiatry. 2014;205(5):383-389.

Dumont GJ, Sweep FC, van der Steen R, Hermsen R, Donders AR, Touw DJ, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. Soc Neurosci. 2009;4:359–366.

Edinoff AN, et al. Benzodiazepines: Uses, Dangers, and Clinical Considerations. Neurol Int. 2021 Nov 10;13(4):594-607.

Edmondson D, von Känel R. Post-traumatic stress disorder and cardiovascular disease. The Lancet Psychiatry. 2017 Apr 1;4(4):320-9.

Eftekhari A, Ruzek JI, Crowley JJ, Rosen CS, Greenbaum MA, Karlin BE. Effectiveness of national implementation of prolonged exposure therapy in Veterans Affairs care. JAMA Psychiatry. 2013 Sep;70(9):949-955.

Fallon JK, et al. Action of MDMA (ecstasy) and its metabolites on arginine vasopressin release. Ann N Y Acad Sci, 2002;965:399-409.

Farré M, et al. Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 4 h apart Human pharmacology of MDMA after repeated doses taken 4 h apart. Eur Neuropsychopharmacol. 2015 Oct;25(10):1637-1649.

FDA. Psychedelic Drugs: Considerations for Clinical Investigations [guidance document]. June 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations.

Ferrario CR, Gorny G, Crombag HS, Li Y, Kolb B, Robinson TE. Neural and behavioral plasticity associated with the transition from controlled to escalated cocaine use. Biol Psychiatry. 2005 Nov 1;58(9):751-759.

Foa, E.B., et al., Effective Treatments for PTSD, Practice Guidelines from the International Society for Traumatic Stress Studies. Second ed. 2009, New York, NY: Guilford Press.

Foderaro LW. Psychedelic Drug Called Ecstasy Gains Popularity in Manhattan Nightclubs. New York Times. December 11, 1988, Section 1, Page 58.

Francis SM, Kirkpatrick MG, de Wit H, Jacob S. Urinary and plasma oxytocin changes in response to MDMA or intranasal oxytocin administration. Psychoneuroendocrinology. 2016;74:92–100.

Freudenmann RW, Öxler F, Bernschneider-Reif S. The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. Addiction, 2006. 101(9):1241-1245.

Gabriel M, Sharma V. Antidepressant discontinuation syndrome. CMAJ. 2017 May 29;189(21):E747.

Galovski T and Lyons JA. Psychological sequelae of combat violence: A review of the impact of PTSD on the veteran's family and possible interventions. Aggress Violent Behav. 2004;9(5):477-501.

Goetter EM, et al. Barriers to mental health treatment among individuals with social anxiety disorder and generalized anxiety disorder. Psychol Serv. 2020 Feb;17(1):5-12.

Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, Pickering RP, Ruan WJ, Huang B, Grant BF. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Soc Psychiatry Psychiatr Epidemiol. 2016 Aug;51(8):1137-48.

Greer GR, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs. 1986;18(4):319-327.

Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. J Psychoactive Drugs, 1998;30(4):371-379.

Grob CS, Poland RE, Chang L, Ernst T. Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. Behav Brain Res. 1996;73(1-2):103-107.

Grob C. MDMA research: preliminary investigations with human subjects. International Journal of Drug Policy. Volume 9, Issue 2, 1 April 1998, p. 119-124.

Haagen JF, Smid GD, Knipscheer JW, et al. The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. Clinical Psychology Review 2015;40: 184-194.

Hake HS, Davis JKP, Wood RR, et al. 3,4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. Physiol Behav. 2019;199: 343-350.

Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT. Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology (Berl). 2002 Aug;162(4):396-405.

Hartman RL, et al. 3,4-Methylenedioxymethamphetamine (MDMA) and metabolites disposition in blood and plasma following control oral administration, Anal Bioanal Chem. 2014; 406(1):587-599.

Haviland MG, Banta JE, Sonne JL, Przekop P. Posttraumatic Stress Disorder-Related Hospitalizations in the United States (2002-2011): Rates, Co-Occurring Illnesses, Suicidal Ideation/Self-Harm, and Hospital Charges. J Nerv Ment Dis. 2016;204(2):78-86.

Helmlin HJ, et al. Analysis of 3,4-methylenedioxymethamphetamine (MDMA) and its metabolites in plasma and urine by HPLC-DAD and GC-MS. J Anal Toxicol. 1996;20(6):432-440.

Hoge CW, Grossman SH, Auchterlonie JL, et al. PTSD treatment for soldiers after combat deployment: Low utilization of mental health care and reasons for dropout. Psychiatric services. 2014;65(8): 997-1004.

Holze F, Vizeli P, Müller F, et al. Distinct acute effects of LSD, MDMA, and d-Amphetamine in healthy subjects. Neuropsychopharmacology. 2020 Feb;45(3):462-471.

Horvath AO, Del Re AC, Flückiger C, Symonds D. Alliance in individual psychotherapy. Psychotherapy. 2011 Mar;48(1):9.

Hysek CM, Simmler LD, Ineichen M, Grouzmann E, Hoener MC, Brenneisen R, et al. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA (“ecstasy”) in humans. Clin Pharm Ther. 2011;90:246-255.

Hysek CM, Simmler LD, Nicola V, Vischer N, Donzelli M, Krähenbühl S, et al. Duloxetine inhibits effects of MDMA (“ecstasy”) in vitro and in humans in a randomized placebo-controlled laboratory study. PLoS ONE. 2012;7:e36476.

Hysek CM, et al. MDMA enhances emotional empathy and prosocial behavior. Social cognitive and affective neuroscience. 2014;9(11):1645-1652.

Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. Am J Psychiatry. 2001 Aug;158(8):1184-1190.

Kantor V, Knefel M, Lueger-Schuster B. Perceived barriers and facilitators of mental health service utilization in adult trauma survivors: A systematic review. Clinical Psychology Review. 2017;52: 52-68.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593-602.

Kessler RC, Aguilar-Gaxiola S, Alonso J, et al. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatol. 2017 Oct 27;8(sup5):1353383. doi: 10.1080/20008198.2017.1353383. PMID: 29075426; PMCID: PMC5632781.

Kirkpatrick MG, et al. Plasma oxytocin concentrations following MDMA or intranasal oxytocin in humans. Psychoneuroendocrinology, 2014a. 46: p. 23-31.

Kirkpatrick MG, Lee R, Wardle MC, Jacob S, de Wit H. Effects of MDMA and intranasal oxytocin on social and emotional processing. Neuropsychopharmacology. 2014b;39:1654-1656.

Koenen KC, Ratanatharathorn A, Ng L, et al. Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med. 2017 Oct;47(13):2260-2274.

Kolbrich EA, Goodwin RS, Gorelick DA, Hayes RJ, Stein EA, Huestis MA. Plasma pharmacokinetics of 3,4-methylenedioxymethamphetamine after controlled oral administration to young adults. Therapeutic drug monitoring. 2008a;30(3):320-332.

Kolbrich EA, Goodwin RS, Gorelick DA, Hayes RJ, Stein EA, Huestis MA. Physiological and subjective responses to controlled oral 3,4-methylenedioxymethamphetamine administration. J Clin Psychopharmacol. 2008b;28(4):432-440.

Krystal JH, et al. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry. 2017 Oct 1;82(7):e51-e59.

Lanteri C, Doucet EL, Hernández Vallejo SJ. Repeated exposure to MDMA triggers long-term plasticity of noradrenergic and serotonergic neurons. Mol Psychiatry. 2014 Jul;19(7):823-833.

Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. Psychotherapy versus pharmacotherapy for post-traumatic stress disorder: systemic review and meta-analyses to determine first-line treatments. Depress Anxiety. 2016;33(9):792-806.

Leon AC, Olfson M, Portera L, et al. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J Psychiatry Med. 1997;27(2):93-105.

Lewis C, Roberts NP, Gibson S, et al. Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: systematic review and meta-analysis. Eur J Psychotraumatol. 2020;11(1):1709709.

Lichtigfeld FJ, Gillman MA. Antidepressants are not drugs of abuse or dependence. Postgrad Med J. 1998 Sep;74(875):529 532.

Liechti ME, Baumann C, Gamma A, Vollenweider FX. Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) are attenuated by the serotonin uptake inhibitor citalopram. Neuropsychopharmacology. 2000a;22:513-521.

Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX. Psychological and physiological effects of MDMA (“ecstasy”) after pretreatment with the 5-HT2 antagonist ketanserin in healthy humans. Neuropsychopharmacology. 2000b;23:396-404.

Liechti ME, Gamma A, Vollenweider FX. Gender differences in the subjective effects of MDMA. Psychopharmacology (Berl). 2001 Mar 1;154(2):161-168.

Lizarraga LE, Cholanians AB, Phan AV, Herndon JM, Lau SS, Monks TJ. Vesicular monoamine transporter 2 and the acute and long-term response to 3,4 (±) methylenedioxymethamphetamine. Toxicol Sci. 2015 Jan;143(1):209-219.

Lukaschek K, et al. Relationship between posttraumatic stress disorder and type 2 diabetes in a population-based cross-sectional study with 2970 participants. J Psychosom Res. 2013;74(4):340-345.

Maples-Keller JL, Norrholm SD, Burton M, et al. A randomized controlled trial of 3,4-methylenedioxymethamphetamine (MDMA) and fear extinction retention in healthy adults. J Psychopharmacol. 2022;36(3): 368-377.

Marie N, Canestrelli C, Noble F. Transfer of neuroplasticity from nucleus accumbens core to shell is required for cocaine reward. PLoS One. 2012;7(1):e30241.

Mas M, et al. Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. J Pharmacol Exp Ther. 1999;290(1):136-145.

Metzner R and Adamson S. Using MDMA in healing, psychotherapy, and spiritual practice, in Ecstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA., J. Holland, Editor. 2001, Inner Traditions: Rochester VT. p. 182-207.

Mithoefer M, Mithoefer A, Jerome L, et al. A manual for MDMA-assisted psychotherapy in the treatment of posttraumatic stress disorder; Version 8. 2017. http://www.maps.org/research/mdma/mdma-research-timeline/4887-a-manual-for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd.

Mithoefer MC, Mithoefer AT, Feduccia AA, et al. "3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial." Lancet Psychiatry, 2018;5(6): 486-497.

Mott JM, Mondragon S, Hundt NE, Beason-Smith M, Grady RH, Teng EJ. Characteristics of U.S. veterans who begin and complete prolonged exposure and cognitive processing therapy for PTSD. J Trauma Stress. 2014 Jun;27(3):265-273.

Najavits LM. The problem of dropout from “gold standard” PTSD therapies. F1000Prime Rep. 2015;7: 43.

Nardou R, Lewis EM, Rothhaas R, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature, 2019. 569(7754): p. 116-120.

National Center for PTSD – US Department of Veterans Affairs: https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp

Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. Journal of psychoactive drugs. 1986 Oct 1;18(4):305-13.

Nichols DE. Entactogens: How the Name for a Novel Class of Psychoactive Agents Originated. Front Psychiatry. 2022 Mar 25;13:863088.

Nichter B, Norman S, Haller M, Pietrzak RH. "Psychological burden of PTSD, depression, and their comorbidity in the U.S. veteran population: Suicidality, functioning, and service utilization." J Affect Disord. 2019;256: 633-640.

Nock MK, et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. PloS Med. 2009;6(8):e1000123.

O'Mathúna B, Farré M, Rostami-Hodjegan A, et al. The consequences of 3,4-methylenedioxymethamphetamine induced CYP2D6 inhibition in humans. J Clin Psychopharmacol. 2008 Oct;28(5):523-529.

Ot'alora GM, Grigsby J, Poulter B, et al. "3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial." J Psychopharmacol 2018;32(12): 1295-1307.

Panagioti M, Gooding PA, Tarrier N. A meta-analysis of the association between post-traumatic stress disorder and suicidality: the role of comorbid depression. Compr Psychiatry. 2012;53(7):915-930.

Passie T, Benzenhöfer U. The History of MDMA as an Underground Drug in the United States, 1960-1979. J Psychoactive Drugs. 2016 Apr-Jun;48(2):67-75.

Passie T. The early use of MDMA (‘Ecstasy’) in psychotherapy (1977–1985). Drug Science, Policy and Law. 2018 Apr;4:2050324518767442.

Peiro AM, et al. Human pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) after repeated doses taken 2 h apart. Psychopharmacology. 2013;225(4):883-893.

Pentney AR. An exploration of the history and controversies surrounding MDMA and MDA. Journal of psychoactive drugs. 2001 Sep 1;33(3):213-221.

Pfizer Inc. Zoloft [prescribing information]. New York, NY: Roerig Division of Pfizer Inc.; 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/19-839S026_Zoloft_Clinr_P1.pdf.

Ramos L, Hicks C, Kevin R, Caminer A, Narlawar R, Kassiou M, et al. Acute prosocial effects of oxytocin and vasopressin when given alone or in combination with 3,4-methylenedioxymethamphetamine in rats: involvement of the V1A receptor. Neuropsychopharmacology. 2013;38:2249 2259.

Rodriguez BF, Weisberg RB, Pagano ME, et al. Mental health treatment received by primary care patients with posttraumatic stress disorder. J Clin Psychiatry. 2003 Oct;64(10):1230-6. doi: 10.4088/jcp.v64n1014. PMID: 14658973; PMCID: PMC3278912.

Ricou M, Marina S, Vieira PM, Duarte I, Sampaio I, Regalado J, Canário C. Psychological intervention at a primary health care center : predictors of success. BMC Family Practice. 2019 Dec;20(1):1-8.

Rudnick G, Wall SC. The molecular mechanism of "ecstasy" [3,4-methylenedioxy-methamphetamine (MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. Proc Natl Acad Sci U S A. 1992 Mar 1;89(5):1817-21.

Sareen J, Jacobi F, Cox BJ, Belik S, Clara I, Stein MB. Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. Arch Intern Med. 2006;166(19):2109-2116.

Schenk S, Gittings D, Colussi-Mas J. Dopaminergic mechanisms of reinstatement of MDMA-seeking behaviour in rats. Br J Pharmacol. 2011 Apr;162(8):1770-1780.

Schenk S, Highgate Q. Methylenedioxymethamphetamine (MDMA): Serotonergic and dopaminergic mechanisms related to its use and misuse. J Neurochem. 2021 Jun;157(5):1714-1724.

Scherrer JF, et al. Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans Administration patients. Am Heart J. 2010;159(5):772-779.

Schmid Y, et al. Interactions between bupropion and 3,4-methylenedioxymethamphetamine in healthy subjects. J Pharmacol Exp Ther. 2015;353(1):102-111.

Schmid Y, et al. CYP2D6 function moderates the pharmacokinetics and pharmacodynamics of 3,4-methylene-dioxymethamphetamine in a controlled study in healthy individuals. Pharmacogenet Genomics. 2016 Aug;26(8):397-401.

Schmid Y, et al. CYP2D6 function moderates the pharmacokinetics and pharmacodynamics of 3,4-methylene-dioxymethamphetamine in a controlled study in healthy individuals – Supplemental Materials. Pharmacogenet Genomics. 2016 Aug;26(8):397-401.

Schnurr PP, et al. Comparison of Prolonged Exposure vs Cognitive Processing Therapy for Treatment of Posttraumatic Stress Disorder Among US Veterans: A Randomized Clinical Trial. JAMA Netw Open. 2022;5(1):e2136921.

Schindler CW, et al. Effects of 3,4-methylenedioxymethamphetamine (MDMA) and its main metabolites on cardiovascular function in conscious rats. Br J Pharmacol. 2014;171(1):83-91.

Schwaninger AE, et al. Urinary excretion kinetics of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and its phase I and phase II metabolites in humans following controlled MDMA administration. Clin Chem. 2011;57(12):1748-1756.

Segura M, et al. Contribution of cytochrome P450 2D6 to 3,4-methylenedioxymethamphetamine disposition in humans: use of paroxetine as a metabolic inhibitor probe. Clinical pharmacokinetics. 2005;44(6):649-660.

Seligowski AV, Webber TK, Marvar PJ, Ressler KJ, Philip NS. Involvement of the brain–heart axis in the link between PTSD and cardiovascular disease. Depression and anxiety. 2022 Oct;39(10-11):663-74.

Shalev A, Liberzon I, Marmar C. Post-traumatic stress disorder. N Engl J Med. 2017;376(25):2459-2469.

Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol. 2008 Mar;23(2):70-83.

Shulgin AT, Nichols DE. Characterization of three new psychotomimetics, in The Pharmacology of Hallucinogens, R.C. Stillman and R.E. Willette, Editors. 1978, Pergamon: New York.

Siegel RK. MDMA. Nonmedical use and intoxication. J Psychoactive Drugs. 1986 Oct-Dec;18(4):349-354.

Simiola V, Neilson E, Thompson R, Cook JM. Preferences for trauma treatment: A systematic review of the empirical literature. Psychol Trauma. 2015;7(6):516-524.

Simmler LD, Buser TA, Donzelli M, et al. Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol. 2013 Jan;168(2):458-470.

Sottile RJ, Vida T. A proposed mechanism for the MDMA-mediated extinction of traumatic memories in PTSD patients treated with MDMA-assisted therapy. Front Psychiatry. 2022 Oct 12;13:991753.

Sumnall HR, Cole JC, Jerome L. The varieties of ecstatic experience: an exploration of the subjective experiences of ecstasy. J Psychopharmacol, 2006. 20(5): p. 670-682.

Swift JK, Callahan JL. The impact of client treatment preferences on outcome: a meta-analysis. J Clin Psychol. 2009 Apr;65(4):368-381.

Stanley IH. Advancements in the understanding of PTSD and suicide risk: Introduction to a special section. Psychol Trauma. 2021;13(7):723-724.

Steenkamp MM, Litz BT, Hoge CW, Marmar CR. Psychotherapy for military-related PTSD: a review of randomized clinical trials. JAMA. 2015;314(5):489-500.

Stefanovics EA, Potenza MN, Pietrzak RH. PTSD and obesity in US military veterans: Prevalence, health burden, and suicidality. Psychiatry Res. 2020;291:1132-1142.

Steuer AE, et al. Chiral Plasma Pharmacokinetics of 3,4-Methylenedioxymethamphetamine and its Phase I and II Metabolites following Controlled Administration to Humans. Drug Metab Dispos. 2015a;43(12):1864-1871.

Steuer AE, et al. Development and validation of an LC-MS/MS method after chiral derivatization for the simultaneous stereoselective determination of methylenedioxy-methamphetamine (MDMA) and its phase I and II metabolites in human blood plasma. Drug Test Anal. 2015b;7(7):592-602.

Tancer M, Johanson CE. Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP. Drug Alcohol Depend, 2003. 72(1): p. 33-44.

Tarrier N, Gregg L. Suicide risk in civilian PTSD patients-predictors of suicidal ideation, planning and attempts. Soc Psychiatry Psychiatr Epidemiol. 2004;39(8):655-661.

Thabet AA, Vostanis P. Post-traumatic stress reactions in children of war. J Child Psychol Psychiatry. 1999;40(3):385-391.

Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT1A receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ("ecstasy"). Neuroscience. 2007;146:509-514.

Tiangco DA, et al. 3,4-methylenedioxymethamphetamine activates nuclear factor-kappaB, increases intracellular calcium, and modulates gene transcription in rat heart cells. Cardiovasc Toxicol. 2005;5(3):301-310.

United Nations Office on Drugs and Crime (UNODC). World Drug Report. 2023. New York, New York. 2023, Jun. https://www.unodc.org/unodc/en/data-and-analysis/world-drug-report-2023.html

Unternaehrer EA, Meyer AH, Burkhardt SC, et al. Childhood maternal care is associated with DNA methylation of the genes for brain-derived neurotrophic factor (BDNF) and oxytocin receptor (OXTR) in peripheral blood cells in adult men and women. Stress. 2015;18(4): 451-461.

US Department of Justice, Drug Enforcement Administration (DEA). Schedules of Controlled Substances: Temporary Placement of 3,4 Methylenedioxymethamphetamine (MDMA) into Schedule I. Washington D.C. 1985. Electronic version of printed copy available at: https://maps.org/wp-content/uploads/1988/11/0196.pdf.

US Department of Justice, Drug Enforcement Administration (DEA). Schedules of Controlled Substances: In the Matter of MDMA Scheduling: Opinion and Recommended Ruling, Findings of Fact, Conclusions of Law and Decision of Administrative Law Judge. Washington D.C. 1986a. Electronic version of printed copy available at: https://maps.org/wp-content/uploads/1988/11/0112.pdf.

US Department of Justice, Drug Enforcement Administration (DEA). Schedules of Controlled Substances: In the Matter of MDMA Scheduling: Government's Exceptions to the Opinion and Recommended Rulings, Findings of Fact, Conclusions of law and decision of the Administrative Law Judge. Washington D.C. 1986b. Electronic version of printed copy available at: https://maps.org/wp-content/uploads/1988/11/0113.pdf.

US Department of Justice, Drug Enforcement Administration (DEA). Schedules of Controlled Substances: Scheduling of 3,4 Methylenedioxymethamphetamine (MDMA) into Schedule I of the Controlled Substances Act. Washington D.C. 1988. https://www.govinfo.gov/app/details/FR-1988-02-22.

US Department of Veterans Affairs. Veterans Benefits Report Fiscal Year 2023. 2024. http://benefits.va.gov/REPORTS/abr/: VA Benefits Administration.

VA/DOD. Clinical Practice Guideline for the Management of Post-traumatic Stress Disorder and Acute Stress Disorder. 2023. https://www.healthquality.va.gov/guidelines/MH/ptsd/VA-DoD-CPG-PTSD-Full-CPGAug242023.pdf.

VA National Center for PTSD. US Department of Veterans Affairs. Accessed February 14, 2023. https://www.ptsd.va.gov/understand/common/common_adults.asp.

Van Ameringen M, Mancini C, Patterson B, Boyle MH. Post-traumatic stress disorder in Canada. CNS Neurosci Ther 2008 Fall;14(3):171-181.

Varker T, Kartal D, Watson L, Freijah I, O'Donnell M, Forbes D, Phelps A, Hopwood M, McFarlane A, Cooper J, Wade D. Defining response and nonresponse to posttraumatic stress disorder treatments: A systematic review. Clinical Psychology: Science and Practice. 2020 Dec;27(4):e12355.

Verrico CD, Miller GM, and Madras BK. MDMA (Ecstasy) and human dopamine, norepinephrine, and serotonin transporters: implications for MDMA-induced neurotoxicity and treatment. Psychopharmacology (Berl). 2007;189(4):489-503.

Vizeli P, ME Liechti. Safety pharmacology of acute MDMA administration in healthy subjects. J Psychopharmacol. 2017;31(5):576-588.

Vollenweider FX, et al. Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naïve healthy volunteers. Neuropsychopharmacology. 1998;19(4):241-251.

Wardle MC and de Wit H. MDMA alters emotional processing and facilitates positive social interaction. Psychopharmacology. 2014; (Berl) 231(21): 4219-4229.

Wardle MC, Kirkpatrick MG, de Wit H. Ecstasy' as a social drug: MDMA preferentially affects responses to emotional stimuli with social content. Soc Cogn Affect Neurosci. 2014; 9(8): 1076-1081.

Weathers FW, Litz BT, Keane TM, et al. The PTSD checklist for DSM-5 (pcl-5), 2013.

Weathers FW, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and Initial Psychometric Evaluation in Military Veterans. Psychol Assess, 2017.

Weathers FW, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess. 2018;30(3):383-395.

Yehuda R, et al. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015;1:150-157.

Young MB, Andero R, Ressler KJ, et al. 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. Transl Psychiatry. 2015;5: e634.

Yubero-Lahoz S, Ayestas MA Jr, Blough BE, Partilla JS, Rothman RB, de la Torre R, Baumann MH. Effects of MDMA and related analogs on plasma 5-HT: relevance to 5-HT transporters in blood and brain. Eur J Pharmacol. 2012 Jan 15;674(2-3):337-344.

Yubero-Lahoz S, Pardo R, Farré M, et al. Sex differences in 3,4methylenedioxymethamphetamine (MDMA; ecstasy)-induced cytochromeP450 2D6 inhibition in humans. Clinical pharmacokinetics. 2011; 50(5):319–329.

11 APPENDICES

11.1 Clinical Studies Supporting the Safety of MDMA

Clinical studies supporting the safety of MDMA are summarized in Table 29.

Six studies in which MDMA was administered to participants with PTSD were pooled for the safety analyses. The decision to include studies in the pooled analysis groups was based on a number of factors, including the patient populations and clinical relevance to the target PTSD populations, similarity of study designs, MDMA treatment regimens and dosing strategies, control groups, the number of MDMA-treated participants, and the safety parameters assessed in the studies (specifically, the collection of AEs).

- The All Pooled Group: Included participants from 6 Phase 2 or 3 studies.
    - 2 pivotal placebo-controlled Phase 3 PTSD studies (MAPP1 and MAPP2)
    - 2 double-blind (DB), active-controlled Phase 2 studies evaluating multiple MDMA dose regimens, with Open Label (OL) dosing periods (MP-8 and MP-12)
    - 2 OL studies: Phase 2 OL study MP16, and the ongoing extension study to MAPP1 and MAPP2, MAPPUSX
- Three additional Pooling Groups, each included 2 or more of the studies included in the All Pooled group.
    - Pooled Phase 3: Includes participants in the pivotal trials MAPP1 and MAPP2.
    - Second pooling group: Includes participants in the 2 pivotal trials, the extension study MAPPUSX, and the Phase 2 study MP16.
    - Third pooling group: Includes the 2 Phase 2 studies MP-8 and MP-12.

Table 29: Clinical Studies Supporting the Safety of MDMA

Study Study Dates Status	Country/ Study Phase	Population	Study Design	MDMA Dose Regimen	Treatment Groups (Treated/Completed, n[a])	Safety Assessments
MAPP1 21 Nov 2018 – 21 Aug 2020 Completed, CSR finalized	US, Israel, and Canada/ Phase 3	Severe PTSD	• Multi-site (15 sites) • Randomized • Double-blind • Placebo-controlled • 3 MDMA (or placebo) experimental sessions[b]	• ES1: 120 mg (80 + 40 mg) • ES2: 180 mg (120 + 60 mg) • ES3: 180 mg (120 + 60 mg)	• MDMA: 46/42 • Placebo: 44/37	• AE • SAE • AESI • C-SSRS • Vital Signs[c] • Concomitant medications
MAPP2 10 Dec 2020 – 02 Nov 2022 Completed, CSR finalized	US and Israel Phase 3	Moderate or greater PTSD	• Multi-site (13 sites) • Randomized • Double-blind • Placebo-controlled • 3 MDMA (or placebo) experimental sessions[b]	• ES1: 120 mg (80 + 40 mg) • ES2: 180 mg (120 + 60 mg) • ES3: 180 mg (120 + 60 mg)	• MDMA: 53/53 • Placebo: 51/43	• AE • SAE • AESI • C-SSRS • Vital Signs[c] • Concomitant medications
MP16 24 Oct 2017 – 10 Aug 2019 Completed, CSR finalized	US/ Phase 2	Severe PTSD	• Multi-site (12 sites) • OL lead-in study • 3 MDMA experimental sessions to Phase 3	• ES1: 120 mg (80 + 40 mg) • ES2: 180 mg (120 + 60 mg) • ES3: 180 mg (120 + 60 mg)	• MDMA: 33/32	• AE • SAE • AESI • C-SSRS • Vital signs • Concomitant medications
MAPPUSX 08 Mar 2021 – Ongoing, interim analysis data cutoff date 12 Dec 2022	US, Israel, and Canada/ Phase 3 extension	• History of moderate to severe PTSD • Treated with placebo in MAPP1/MAPP2 • MAPP1/MAPP2 participants affected by early study closure or unforeseen circumstances[d]	• Multi-site (15 sites) • OL extension study	• ES1: 120 mg (80 + 40 mg)[e] • ES2: 180 mg (120 + 40 or 60 mg) • ES3: 180 mg (120 + 40 or 60 mg)	• MDMA: 41/30[f] • Prior study/treatment • MAPP1 Placebo: 32 • MAPP1 MDMA: 1 • MAPP1/MAPP2 enrollment confirmation failures: 8	• AE • SAE • AESI • C-SSRS • Vital signs • Concomitant medications

Study Study Dates Status	Country/ Study Phase	Population	Study Design	MDMA Dose Regimen	Treatment Groups (Treated/Completed, n[a])	Safety Assessments
MP-8 10 Nov 2010 – 25 Oct 2016 Completed, CSR finalized	US/ Phase 2	• Moderate to severe PTSD • Veterans, firefighters, or police officers	• Single site Stage 1 • Active control • Randomized • Triple-blind[g] • 2 Blinded MDMA or control experimental sessions • 1 OL experimental session Stage 2 • OL extension for Stage 1 low and medium dose groups • Additional 3 MDMA treatment sessions[b] • LTFU (12 months)	Stage 1 Low dose • ES1, ES2, ES3: 45 mg (30 + 15 mg) Medium dose • ES1, ES2, ES3: 112.5 mg (75 + 37.5 mg) High dose: • ES1, ES2, ES3: 187.5 mg (125 + 62.5 mg) Stage 2 • ES4: 100-150 mg (100 + 50 mg)[h] • ES5, ES6: 125-187.5 mg (100-125 mg + 12.5-50 mg)[h]	Stage 1 • Low: 7/6 • Medium: 7/6 • High: 12/12 • Total: 26/24 Stage 2 • MDMA (Stage 1 low): 6/6 • MDMA (Stage 1 medium): 6/6 • Total: 12/12	• AE • SAE • SRR • C-SSRS • Vital signs • SUD • VAS (pre-existing tinnitus, chronic pain)
MP-12 13 May 2013 – 01 Feb 2017 Completed, CSR finalized	US/ Phase 2	Moderate to severe, treatment-resistant, chronic PTSD	• Single site Stage 1 • Active control • Randomized • Double-blind[g] • 2 Blinded MDMA or control experimental sessions • 1 OL ES[b] Stage 2 • OL extension for Stage 1 comparator dose (low) group • Additional 3 MDMA treatment sessions[b] • LTFU (12 months)	Stage 1 MDMA low • ES1, ES2: 40-60 mg (40 + 20 mg) MDMA dose 2 (medium) • ES1, ES2: 100-150 mg (100 + 50 mg • ES3: 100-187.5 mg (100 or 125 + 50 or 62.5 mg) ES3: 150 mg (100 +50 mg) MDMA dose 1 (high) • ES1, ES2, ES3: 187.5 mg (125 + 62.5 mg) Stage 2 • ES4: 100-150 mg (100 + 50 mg)[h,i],	Stage 1 • MDMA Low Dose: 6/5 • MDMA Dose 2: 9/9 • MDMA Dose 1: 13/12 • Total: 28/26 • Stage 2: • MDMA: 5/4	• AE • SAE • SRR • C-SSRS • Vital signs • SUD • RBANS • PASAT • VAS (pre-existing tinnitus, chronic pain)

Study Study Dates Status	Country/ Study Phase	Population	Study Design	MDMA Dose Regimen	Treatment Groups (Treated/Completed, n[a])	Safety Assessments
				• ES5, ES6: 125-187.5 mg (100-125 mg +/- 12.5 – 50 mg)[h]		
MPLONG 01 Mar 2021 – 21 May 2023 Completed; Interim CSR	US, Israel, and Canada/ LTFU	• History of moderate or greater PTSD • Participants must have completed 1 experimental session in a sponsored study to be eligible	• Multi-site (3 sites) • Non-interventional LTFU	Not applicable	• 151 participants enrolled at time of interim analysis: • 133 completed • 9 ongoing • 9 terminated early	• C-SSRS • Interim medical history • Concomitant medications • Incidence of therapy • Incidence of MDMA or ecstasy use
MP17 13 Mar 2018 – 04 Jun 2019 Completed, CSR finalized	Canada/ Phase 2	Severe PTSD	• Multi-site (2 sites) • OL lead-in to Phase 3 • 3 MDMA experimental sessions	• ES1: 150 mg (100 + 50 mg) • ES2, ES3: 187.5 mg (125 + 62.5 mg)	• MDMA: 4/4	• AE • SAE • AESI • C-SSRS • Vital signs • Concomitant medications
MP-9 17 Jan 2013 – 16 Jul 2017 Competed, CSR finalized	Israel/ Phase 2	Moderate to severe, treatment-resistant chronic PTSD	• Single site **Lead-in** • OL • 2 MDMA experimental sessions **Stage 1** • Active placebo-controlled • Randomized • Double-blind • 2 MDMA or comparator dose experimental sessions **Stage 2** • OL extension for Stage 1 comparator dose • Additional 2 MDMA experimental sessions • LTFU (12 months)	Lead-in MDMA • ES1, ES2: 187.5 mg (125 + 62.5 mg) **Stage 1** Low dose MDMA • ES1, ES2: 37.5 mg (25 + 12.5 mg) MDMA • ES1, ES2: 187.5 mg (125 + 62.5 mg) **Stage 2** • ES3, ES4: 187.5 mg (125 + 62.5 mg)	**Lead in** • MDMA: 2/2 **Stage 1** • Low dose MDMA: 3/3 • MDMA: 5/5 • Total: 8/8 **Stage 2** • MDMA: 2/2	• AE • SAE • SRR • C-SSRS • Vital signs • SUD

Study Study Dates Status	Country/ Study Phase	Population	Study Design	MDMA Dose Regimen	Treatment Groups (Treated/Completed, n[a])	Safety Assessments
MP-4 14 Oct 2014 – 17 Oct 2016 Completed, CSR finalized	Canada/ Phase 2	Moderate to severe treatment-resistant chronic PTSD	• Single site **Stage 1** • Placebo-controlled • Randomized • Double-blind • 2 Blinded MDMA or placebo ESs • 1 OL ES **Stage 2** • OL extension for Stage 1 placebo group • 3 MDMA ESs • LTFU (12 months)	Stage 1 Placebo • ES1, ES2: 0 mg MDMA • ES1, ES2, ES3: 125-187.5 mg (125 + 62.5 mg) **Stage 2** MDMA • ES4: 150 mg (100 + 50 mg) • ES5, ES6: 150 mg (100 + 50 mg) or 187.5 mg (125 + 62.5 mg)	Stage 1 • Placebo: 2/2 • MDMA: 4/4 Stage 2 • MDMA dose: 2/2	• AE • SAE • SRR • C-SSRS • Vital signs • PASAT • RBANS • SUD • VAS (pre-existing tinnitus, chronic pain)
MP-3 17 Jan 2008 – 05 May 2010 Terminated, no CSR. Data in ISS	Israel/ Phase 2	Moderate to severe PTSD	• Single site **Stage 1** • Active placebo-controlled • Randomized • Double-blind • 2 MDMA or active placebo ESs **Stage 2** • OL extension for Stage 1 active placebo group • 2 MDMA ESs • LTFU (2, 6, and 12 month)	Stage 1 Low dose MDMA • ES1, ES2: 37.5 mg (25 + 12.5 mg) MDMA • ES1, ES2: 187.5 mg (125 + 62.5 mg Stage 2 MDMA • ES1, ES2: 187.5 mg (125 + 62.5 mg)	Stage 1 • Low dose MDMA: 2/2 • MDMA: 3/2 Stage 2 • MDMA: 1/1	• AE • SAE • SRR • Vital signs • SUD

Study Study Dates Status	Country/ Study Phase	Population	Study Design	MDMA Dose Regimen	Treatment Groups (Treated/Completed, n[a])	Safety Assessments
MP-2 13 Sep 2006 – 10 Jan 2011 Completed, CSR finalized	Switzerland/ Phase 2	Moderate to severe treatment-resistant PTSD	• Single site **Stage 1** • Active placebo-controlled • Randomized • Double-blind • 3 MDMA or active placebo ESs **Stage 2** • OL extension for Stage 1 active placebo group • 3 MDMA ESs **Stage 3** • OL • Offered to participants who showed insufficient response in Stage 1 or 2 • 2 MDMA ESs	Stage 1 Low dose MDMA • ES1, ES2, ES3: 37.5 mg (25 + 12.5 mg) MDMA • ES1, ES2 ES3: 187.5 mg (125 + 62.5 mg) Stage 2 MDMA • ES1, ES2 ES3: 187.5 mg (125 + 62.5 mg Stage 3 MDMA • ES1, ES2: 187.5 mg (125 + 62.5 mg) or 225 mg (150 + 75 mg)	Stage 1 • Low dose MDMA: 5/4 • MDMA: 9/7 Stage 2 • MDMA: 4/4 Stage 3 • MDMA: 3/3	• AE • SAE • SRR • Vital signs • SUD • Clinical laboratory values
MP1-E2 15 Dec 2010 – 27 Jun 2014 Completed, CSR finalized	US/ Phase 2	Relapsed PTSD Participants were eligible if they participated the MP-1 study and had relapsed	• Single site • MDMA • OL • 1 MDMA ES • LTFU (12 months)	MDMA • ES1: 187.5 mg (125 + 62.5 mg)	• MDMA: 3/3	• AE • SAE • SRR • C-SSRS • Vital signs • SUD
MP-1 12 Mar 2004 – 21 Jun 2010 Completed, CSR finalized	US/ Phase 2	Moderate to severe, chronic, treatment-resistant PTSD	• Single site **Stage 1** • Placebo-controlled • Randomized • Double-blind • 2 Blinded MDMA or placebo ES • 1 OL MDMA ES for participants who were in MDMA group[j] **Stage 2[k]** • OL extension for Stage 1 placebo group	**Stage 1[j]** Placebo • ES1, ES2, ES3: 0 mg MDMA • ES1 ES2, ES3: 187.5 mg (125 + 62.5 mg) **Stage 2** MDMA • ES4 ES5, ES6: 187.5 mg (125 + 62.5 mg)	**Stage 1** • Placebo: 8/8 • MDMA: 15/13 **Stage 2** • MDMA: 7/7	• AE • SAE • SRR • Vital signs • SUD • Liver function • RBANS • PASAT • RCFT • NEO-PI

Study Study Dates Status	Country/ Study Phase	Population	Study Design	MDMA Dose Regimen	Treatment Groups (Treated/Completed, n[a])	Safety Assessments
			• 3 MDMA ESs • LTFU (12 months)			
MPKF 15 Aug 2022 – 05 Dec 2022 Completed, CSR finalized	US/ Phase 1	Healthy volunteers	• Single site • PK study • OL • Randomized sequence, 2 period crossover (≥ 14 days between 2 sessions)	• All participants received a single 120 mg dose of MDMA at Dosing Session 1 and 2	• MDMA: 16/14	• AE • SAE • AESI • C-SSRS • Vital signs • ECG • Clinical laboratory values
MT-1 07 Apr 2011 – 05 Aug 2022 Completed, synoptic CSR finalized	US/ Phase 1	Healthy volunteers who were therapists or researchers engaged in MDMA Therapy Training Program	• Multi-site (2 sites) • Placebo-controlled • Randomized • Double-blind • Crossover • LTFU (2 month) • Participants were randomized to receive either: o Placebo at ES1 and MDMA at ES2 (Placebo-MDMA) o MDMA at ES1 and placebo at ES2 (MDMA-Placebo)	ES1, ES2: • Placebo: 0 mg • MDMA: 160 mg (120 + 40 mg)[l]	• Placebo – MDMA: 54/53 • MDMA – Placebo: 54/54	• AE • SAE • SRR • C-SSRS • Vital signs • SUD • BSI • GWB
MPVA-4 14 Mar 2018 – 01 Aug 2020 Completed, CSR finalized	US/ Phase 1	Healthy volunteers	• Single site • Placebo-controlled • Randomized • Blinded • One MDMA or placebo ES	Day 1 • NA Day 2 • Placebo: 0 mg • MDMA: 100 mg Day 3 • NA	• Placebo: 17/17 • MDMA: 17/17	• AE • SAE • Vital signs • Concomitant medications • O-DEQ • MEQ • PANAS • P-SEMS

Study Study Dates Status	Country/ Study Phase	Population	Study Design	Treatment Groups MDMA Dose Regimen (Treated/Completed, n[a])	Safety Assessments

AE: adverse event; AESI: adverse event of special interest; BL: Baseline; BSI: Brief Symptom Inventory; COVID-19: Coronavirus disease 2019; CSR: clinical study report; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; ES: experimental session (i.e., medication session); GWB: general wellbeing; HCl: hydrochloride; IR: independent rater; ISS: Integrated Summary of Safety; LTFU: long-term follow-up; MAPS: Multidisciplinary Association for Psychedelic Studies; MDMA: 3,4-methylenedioxymethamphetamine; MDMA-AT: MDMA-assisted therapy; MEQ: Mystical Experiences Questionnaire; NEO-PI: Neuroticism-Extroversion-Openness Personality Inventory; O-DEQ: Observer-rated Drug Effect Questionnaire; OL: open-label; PASAT: Paced Auditory Serial Addition Test; PK: pharmacokinetic; P-SEMS: Participant-rated Subjective Effects of MDMA Scale; PTSD: post-traumatic stress disorder; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RCFT: Rey-Osterrieth Complex Figure Test; SAE: serious adverse event; SRR: spontaneously reported reaction; SUD: subjective units of distress; US: United States; VAS: visual analog scale

a. Completed intended dosing regimen.

b. Prospective participants were prescreened for eligibility and underwent 3 Preparatory Sessions (~90 minutes each and ≥ 48 hours apart) with the therapy team to prepare for MDMA-AT, allow for medication tapering, and further assess eligibility. The Treatment Period consisted of 3 experimental sessions, 3 to 5 weeks apart, occurring over a total duration of 9 to 15 weeks Each experimental session consisted of administration of either MDMA-AT or placebo paired with therapy (Visit 5, Visit 10, Visit 15), followed by 3 integrative sessions, and phone follow up. A CAPS-5 assessment (T2 and T3) was administered by a blinded IR via telemedicine 18 to 30 days after the first and second experimental sessions.

c. Vital signs include blood pressure, pulse rate, and body temperature.

d. Participants were eligible for MAPPUSX if they who received placebo in the parent study (crossover) or were unable to randomize (enrollment confirmation failures) or complete treatment due to unforeseen circumstances or early study closure due to COVID-19.

e. Experimental sessions in MAPPUSX were numbered ES1, ES2, and ES3 in tables but listed as ES4, ES5, and ES6 in the listings. Doses are 120 mg (80 + 40 mg) at ES1 and 180 mg (120 + 40 or 60 mg) at ES2 and ES3 during the Treatment Period unless tolerability issues emerge with the first dose or it is refused by the participant. The second part of the split dose in MAPPUSX ES2 and ES3 is one third (40 mg) of the first part of the split dose due to drug supply issues, for a total dose of 160 mg.

f. MAPPUSX is ongoing. As of data cutoff on 12 Dec 2022, 2 participants had terminated the study early. Both discontinued due to AE (1 related AE of recurrence of anxiety and 1 not related AE of concussion).

g. The study consisted of a Stage 1 comprising 2 blinded experimental sessions (ES) (ES1, ES2), a single open-label ES (ES3), and a 12 Month LTFU (post ES3). Only participants who received the full dose in Stage 1 completed the OL ES3. Blinded participants were unblinded one at a time to determine eligibility for additional OL experimental sessions.

h. Optional dose escalation unless tolerability issues emerged, or participant declined.

i. Participants who were treated with the comparator dose regimen in Stage 1 had 2 experimental sessions, then had 3 additional sessions in Stage 2; these sessions were labelled ES 4, 5, and 6.
Second part of the split dose and third OL ES was added in MP-1 CSR Protocol Amendment 3. Six participants in each group treated under this protocol version.

j. Second part of the split dose and third OL ES was added in MP-1 CSR Protocol Amendment 3. Six participants in each group treated under this protocol version.

k. Second stage was added in MP-1 CSR Protocol Amendment 1. Six participants in MDMA group and 2 in placebo group treated under this protocol version.

l. Participants randomized prior to January 2021 in MT-1 received the first part of the split dose of 125 mg of MDMA and a second part of the dose of 62.5 mg

Source: ISS, Table 2

11.2 Additional Description of Preparatory and Integration Treatment

11.2.1 Preparatory Period Before Treatment

During the Preparatory Period, participants underwent 3 Preparatory Sessions (~90 minutes each and ≥ 48 hours apart) of psychotherapy (Visit 1, Visit 2, and Visit 4) with the therapy team to prepare for MDMA-AT, allow for medication tapering, and further assess eligibility. This period was initiated within 12 days of enrollment (V0) and lasted 1 to 11 weeks, depending on medication tapering. Excluded medications were to be tapered in an appropriate fashion to avoid withdrawal effects and were to be discontinued long enough before the first medication session to avoid the possibility of drug interactions and allow for stabilization of any psychiatric perturbations due to pre-study medication washout prior to Baseline (e.g., at least 5 times the half-life of the particular drug or its active metabolites, plus 1 week for stabilization). If necessary, the investigators planned for tapering off and discontinuing any psychiatric medication upon enrollment, in consultation with the prescribing physician.

Excluded psychiatric medications were prohibited until after study termination, except for gabapentin or certain opiates (hydrocodone, morphine, and codeine) if they were taken for pain management and stimulants for Attention Deficit/Hyperactivity Disorder (ADHD) taken at Baseline. If the participant was on stimulants for ADHD at Baseline, they could continue to use them at the same dose and frequency through much of the trial. However, they were required to discontinue use 5 half-lives before each medication session and to not restart for 10 days following each medication session.

If any SSRI, SNRI, MAOI, or other antidepressant was used between medication session 1 and medication session 3, the participant discontinued treatment and continued into follow-up.

To be enrolled in the study, participants had to:

1. Refrain from the use of any psychoactive medication not approved by the research team from Baseline through Study Termination (except for gabapentin or certain opioids for pain control and stimulants for ADHD, as described above).
2. Be willing to comply with all medication requirements per protocol. Medications were only discontinued after enrollment per clinical judgment of the site medical provider in consultation with the prescribing physician.
3. Agree that, for 1 week preceding each medication session, they would refrain from taking any specified herbal supplement (except with prior approval from the research team).
4. Agree that, for 5 half-lives of the medication preceding each medication session, they would refrain from:

a. Taking any nonprescription medications (except for nonsteroidal anti-inflammatory medications or acetaminophen) unless with prior approval of the research team.

b. Taking any prescription medications (except for birth control pills, thyroid hormones, or other medications approved by the research team).

The Baseline CAPS-5 assessment was scheduled to occur after complete washout. The Baseline CAPS-5 assessment (T1) was conducted at Visit 3 via a blinded IR. At Visit 4, final eligibility was determined following review of the Baseline CAPS-5 assessment, and participants were randomized to receive either MDMA or inactive placebo. Following medication washout and preparatory psychotherapy, Baseline CAPS-5 TSS were required to be ≥ 28 (MAPP2; at least moderate) or ≥ 35 (MAPP1; at least severe).

11.2.2 Integration Sessions Following Treatment

After each medication session, three integration sessions took place. Each session consisted of 90 minutes of therapy. Integration sessions could not be less than 48 hours apart.

Treatment 1

- Integration Visit 1.1 (Visit 6): morning after medication session 1 (Visit 5)
- Integration Visit 1.2 (Visit 7): 3 to 14 days after medication session 1 (Visit 5)
- Integration Visit 1.3 (Visit 9): 20 to 34 days after medication session 1 (Visit 5) and 1 to 7 days in advance of medication session 2 (Visit 10). This visit served two purposes: to continue integration and to prepare for the next medication session. The participant also completed the LEC-5 self-report measure.

Treatment 2

- Integration Visit 2.1 (Visit 11): morning after medication session 2 (Visit 10)
- Integration Visit 2.2 (Visit 12): 3 to 14 days after medication session 2 (Visit 10)
- Integration Visit 2.3 (Visit 14): 20 to 34 days after medication session 2 (Visit 10) and 1 to 7 days in advance of medication session 3 (Visit 15). This visit served two purposes: to continue integration and to prepare for the next medication session. The participant also completed the LEC-5 self-report measure.

Treatment 3

- Integration Visit 3.1 (Visit 16): morning after medication session 3 (Visit 15)
- Integration Visit 3.2 (Visit 17): 3 to 14 days after medication session 3 (Visit 15)
- Integration Visit 3.3 (Visit 18): 21 to 35 days after medication session 3 (Visit 15)

This visit was the final integration visit prior to entering the follow-up period. The participant also completed the LEC-5 self-report measure.

During Integration Sessions, the therapists:

- Recorded the session.
- Inquired about any possible changes in health, assessed the participant's mental health and status of any previously recorded AEs, and recorded any new AEs.
- Inquired about concomitant medication use and adherence.
- Administered "Since Last Visit C-SSRS" to determine suicidal risk.
- Discussed and reviewed events that occurred with the participant during the medication session, including thoughts, feelings, and memories. If necessary, the therapists helped the participant reduce any residual psychological distress they were experiencing. The therapists also encouraged the transfer of states of acceptance, feelings of intimacy, closeness, and reduced fear experienced in medication sessions to emotionally threatening everyday situations. The therapists were supportive, validated the experience, and facilitated understanding and emotional clearing.
- Were accessible for additional support via phone or telemedicine if needed.
- At each third integration session, directed the participants to complete the LEC-5.

11.3 Additional Phase 3 Results

De Facto Sensitivity Analysis

A supportive (de facto estimand) analysis and sensitivity analyses of the effects of departures from choices and assumptions made for the primary analysis were tested for the primary efficacy endpoint analysis (de jure estimand).

Worst-Case Sensitivity Analysis

The second sensitivity analysis involved replacing all missing MDMA CAPS-5 measures with the worst value in the MDMA-AT group for the respective visit, and all missing measures in the placebo group were replaced by the best value in the placebo group for the respective visit.

Base-Case Sensitivity Analysis

In the third missing at random (MAR) sensitivity analysis, missing CAPS-5 measures from both treatment groups were replaced with the mean placebo result within each visit.

11.3.1 MAPP1 Primary Endpoint Sensitivity Analysis Results

De Facto Sensitivity Analysis

Similar to the results of the primary analysis, the analysis of the de facto estimand showed a statistically significant difference ($p < 0.0001$) between treatment arms, with a

greater reduction in CAPS-5 TSS at Week 18 in participants who received MDMA (-24.55) compared to placebo (-12.51) (Table 30).

The de facto estimand sensitivity analysis indicated that there was no pattern among the missing data distinguished by treatment group that impacted the results of the primary efficacy analysis of the de jure estimand.

Table 30: MAPP 1 Primary Endpoint Sensitivity Analysis: CAPS-5 Total Severity Scores and Change from Baseline de Facto Model (mITT Set)

Statistics	MDMA-AT N = 46	Placebo + Therapy N = 44
Baseline, n	46	44
Mean (SD)	44.0 (6.01)	44.2 (6.15)
Median (min, max)	43.5 (35, 57)	44.0 (35, 62)
Visit 19 (Primary Endpoint), n	42	40
Mean (SD)	19.5 (13.50)	30.5 (12.56)
Median (min, max)	18.5 (0, 51)	31.0 (2, 55)
Change from Baseline to Visit 19, n	42	40
Mean (SD)	-24.4 (11.57)	-13.2 (11.6)
Median (min, max)	-25.0 (-47, 3)	-15.0 (-35, 7)
LS mean (95% CI)	-24.55 (-28.30, -20.80)	-12.51 (-16.35, -8.66)
LS mean for treatment difference (95% CI)[a]	-12.04 (-17.46, -6.62)	
P-value	p < 0.0001	

CAPS-5: Clinician Administered PTSD Scale for DSM-5; CI: confidence interval; LS: least squares; Max: maximum; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; Min: minimum; mITT: modified intent-to-treat; SD: standard deviation
The *de facto* estimand includes data after participants discontinue treatment.
LS Mean, LS Mean difference, 95% CI and p-value of treatment effect at Visit 19 are from the MMRM model.
Source: Table 14.2.1.1.2

Worst-Case Sensitivity Analysis

In the worst-case sensitivity analysis, the treatment effect was maintained and statistically significant, providing supporting evidence for the validity of the MAR assumption (p = 0.0293).

Base-Case Sensitivity Analysis

The treatment effect was maintained and statistically significant, providing additional supporting evidence for the validity of the MAR assumption (p < 0.0001).

11.3.2 MAPP2 Primary Endpoint Sensitivity Analysis Results

In the supportive analysis, the MMRM analysis of the de facto estimand showed a statistically significant difference (p = 0.0003) between treatment groups, with a greater

reduction in CAPS-5 TSS in participants receiving MDMA (-23.72) compared to placebo (-14.79) (Table 31).

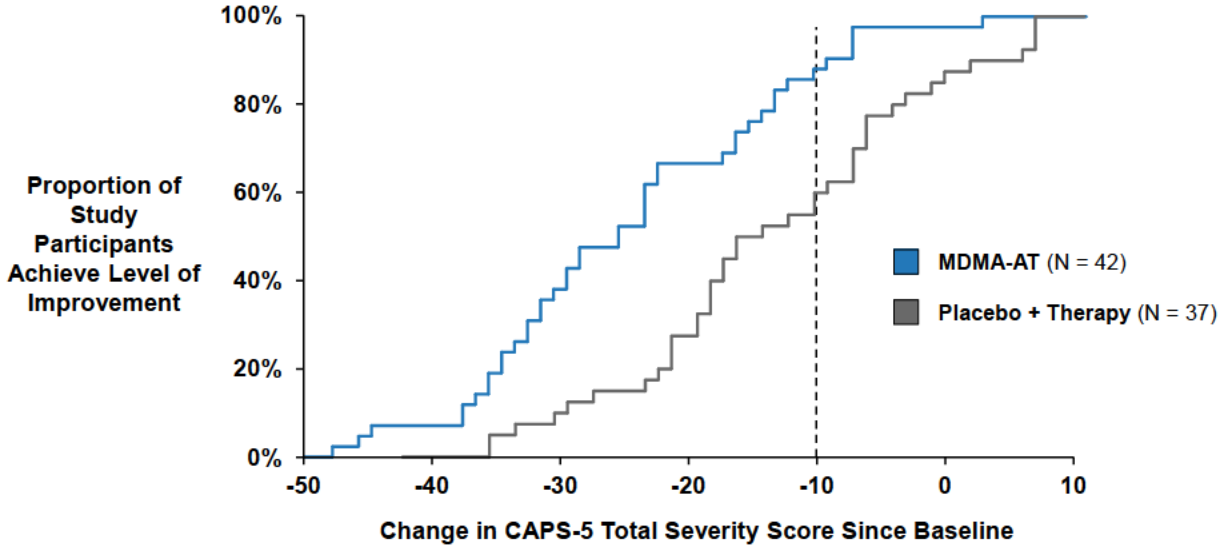
Table 31: MAPP 2 Primary Endpoint Sensitivity Analysis: CAPS-5 Total Severity Scores and Change from Baseline de Facto Model (mITT Set)

Statistics	**MDMA**-AT N = 53	**Placebo + Therapy** N = 50
Baseline, n	53	50
Mean (SD)	39.4 (6.64)	38.8 (6.63)
Median (Min, Max)	39.0 (28, 55)	39.0 (28, 56)
Visit 19 (Primary Endpoint), n	52	44
Mean (SD)	15.8 (12.40)	23.5 (12.69)
Median (Min, Max)	15.5 (0, 44)	21.5 (2, 48)
Change from Baseline to Visit 19, n	52	44
Mean (SD)	-23.5 (12.08)	-15.5 (12.13)
Median (Min, Max)	-25.0 (-44, 9)	-18.0 (-40, 10)
LS Mean (95% CI)	-23.72 (-26.97, -20.47)	-14.79 (-18.24, -11.33)
LS Mean for Treatment Difference (95% CI)	-8.93 (-13.69, -4.17)	
p-value	0.0003	

CAPS-5: Clinician Administered PTSD Scale for DSM-5; CI: confidence interval; LS: least squares; Max: maximum; MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy; Min: minimum; mITT: modified intent-to-treat; SD: standard deviation
The *de facto* estimand includes data after participants discontinue treatment.
Note: LS Mean, LS Mean difference, 95% CI and p-value of treatment effect are from the MMRM model.
Source: Table 14.2.1.1.2.

11.3.3 MAPP1 Primary Efficacy Endpoint Cumulative Responder Plot

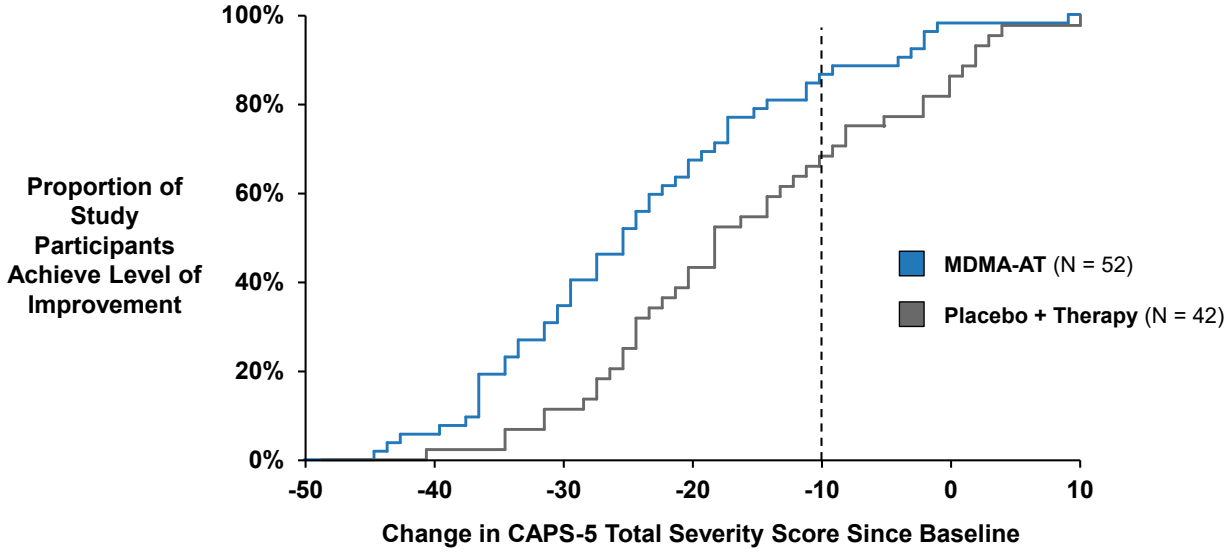
Figure 35: MAPP1 Cumulative Responder Plot of Change from Baseline in CAPS-5 Total Severity Scores at Primary Endpoint



Source: Figure 1a, ADCOM_CAPS_SDS_CDF_HIST_PLOTS_26APR2024

11.3.4 MAPP2 Primary Efficacy Endpoint Cumulative Responder Plot

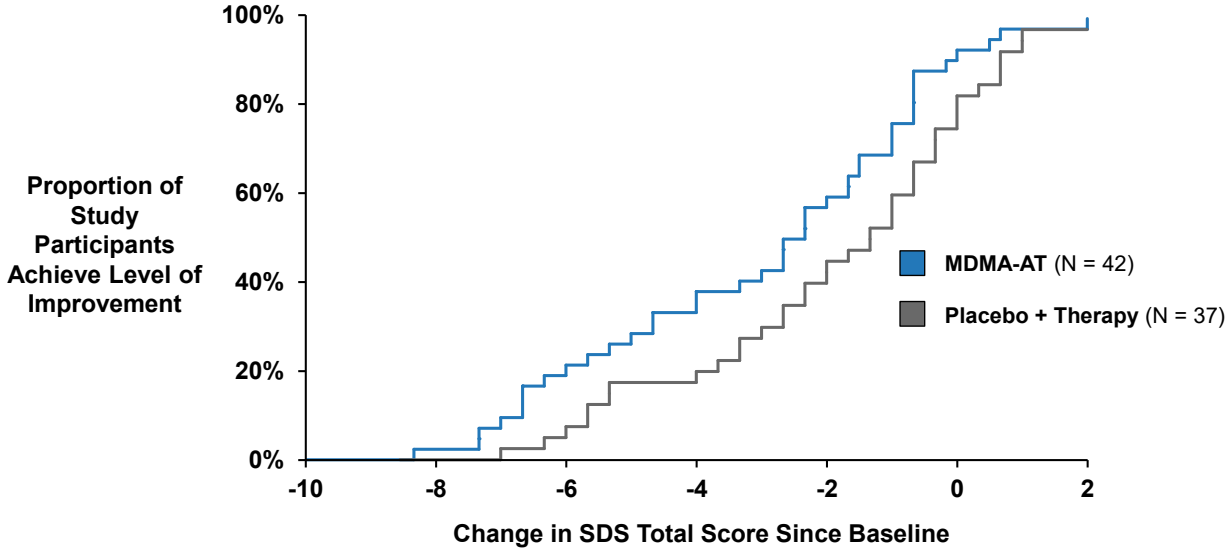
Figure 36: MAPP2 Cumulative Responder Plot of Change from Baseline in CAPS-5 Total Severity Scores at Primary Endpoint



Source: Figure 1a, ADCOM_CAPS_SDS_CDF_HIST_PLOTS_26APR2024

11.3.5 MAPP1 Secondary Efficacy Endpoint Cumulative Responder Plot

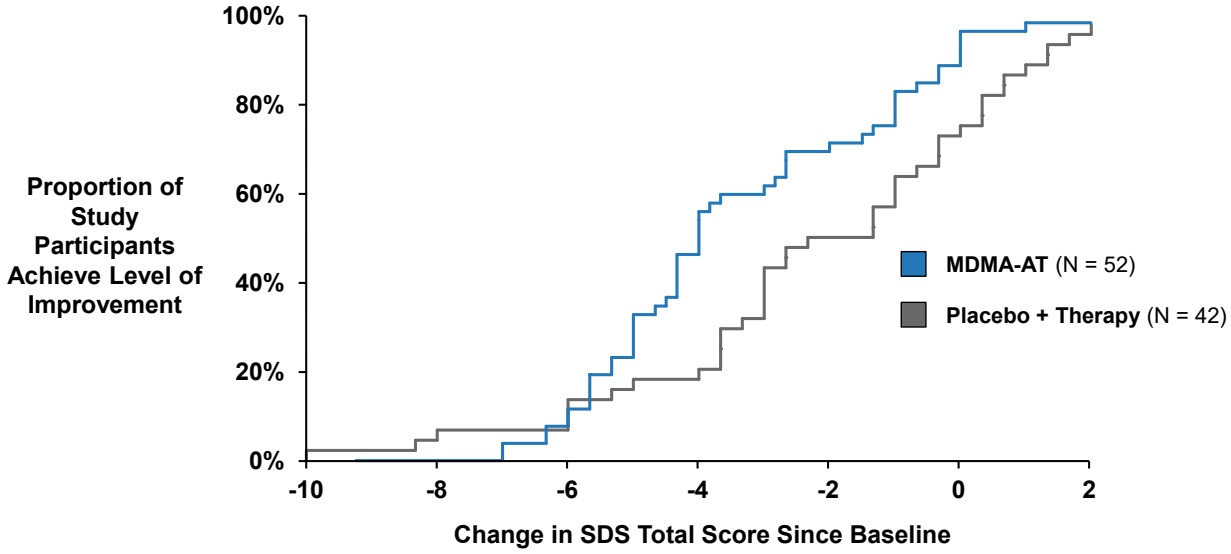
Figure 37: MAPP1 Cumulative Responder Plot of Change from Baseline in SDS Total Scores at Primary Endpoint



Source: Figure 3a, ADCOM_CAPS_SDS_CDF_HIST_PLOTS_26APR2024

11.3.6 MAPP2 Secondary Efficacy Endpoint Cumulative Responder Plot

Figure 38: MAPP2 Cumulative Responder Plot of Change from Baseline in SDS Total Scores at Primary Endpoint



Source: Figure 3b ADCOM_CAPS_SDS_CDF_HIST_PLOTS_26APR2024

11.3.7 Exploratory Endpoint Results Summary

Although p-values were considered descriptive and not confirmatory, they were used to categorize the results from exploratory measures to facilitate conclusions (Table 32). If the p-value was ≤ 0.05 in at least 1 of the 2 studies, MDMA-AT is considered to be suggestive of a treatment effect on that exploratory measure. If the p-value was > 0.05 for both studies, it was stated that the effect of MDMA-AT on that measure was inconclusive.

Of note: the participants in MAPP2 who had at least moderate PTSD would have less opportunity to show improvement because their Baseline scores would be lower than the Baseline scores for those participants who had severe PTSD. In addition, there was a low percentage of study participants that had certain symptoms or comorbidities that were being assessed, despite meeting the inclusion/exclusion criteria (e.g., dissociative subtype), resulting in a potentially underpowered analysis.

Table 32: Conclusions of Exploratory Measures

Category	Measure

Results suggestive of a treatment effect in both studies[a]	• BDI-II
	• CAPS-5 Subscales
	  ○ Re-experiencing
	  ○ Avoidance
	  ○ Negative Alterations in Cognition and Mood
	  ○ Hyperarousal
	  ○ Disturbance causes either clinically significant distress or functional impairment
	• Susceptibility to Influence (IASC)
	• TAS-20
	• SCS
	• EQ-5D-5L[b]

Results suggestive of treatment effect in only 1 study[c]	• Interpersonal Conflicts (IASC) • Idealization-Disillusionment (IASC) • Identity Impairment (IASC) • EAT-26 • HPQSF • IPF
Results inconclusive[d]	• DSP-I • CPGS • Abandonment Concerns (IASC) • Affect Dysregulation (IASC) • Tension Reduction (IASC) • AUDIT • DUDIT • SNRU

P-values were used to facilitate categorization and description of results, but they are not considered confirmatory.
AUDIT: Alcohol Use Disorders Identification Test; BDI-II: Beck Depression Inventory II; CAPS5: Clinician-administered PTSD Scale for DSM-5; CPGS: Chronic Pain Grade Scale; DSPI: Dissociative Subtype of PTSD Interview; DUDIT: Drug Use Disorders Identification Test; EAT26: Eating Attitudes Test; EQ-5D-5L: EuroQol Five Dimensions – Five Levels Questionnaire; HPQSF: Health and Work Performance Absenteeism and Presenteeism Short Form; IASC: Inventory of Altered Self Capacities; IPF: Inventory of Psychosocial Functioning; TAS20: Toronto Alexithymia Scale; SCS: Self-Compassion Scale; SRNU: Self-reported Nicotine Use.
a .Measures in this category had a nominal p-value for treatment effect of ≤ 0.05 in both MAPP1 and MAPP2.
b. Nominal p-value for treatment effect for MAPP1 was 0.0394 and MAPP2 was 0.0557.
c. Measures in this category had a nominal p-value for treatment effect of ≤ 0.05 in only 1 study.
d. Measures in this category had a nominal p-value for treatment effect of > 0.05 in both MAPP1 and MAPP2.
Source: MAPP1-2 Supplemental CSR

11.3.8 Supplemental Blood Pressure and Heart Rate Results

Mean changes in SBP and DBP and HR from predose measurements during each medication session at the interim and end of session timepoints are summarized in Table 33 and Table 34. As described previously, participants were planned to be dosed with 80 mg MDMA followed by 40 mg at medication session 1 and escalated to 120 mg

followed by 60 mg at medication session 2 and medication session 3. In this table, the results for each medication session include all participants dosed at that session, regardless of the dose received. As described previously, almost all participants received the intended dosing at each medication session, i.e., 80 mg followed by 40 mg at the first medication session and 120 mg followed by 60 mg at the second and third medication sessions.

Table 33: Systolic and Diastolic Blood Pressure Results During Medication Sessions (Immediate Effect) (Pooled Phase 3; Safety Set)

	Systolic Blood Pressure		**Diastolic** Blood Pressure	
	MDMA-AT **N =** 99	**Placebo + Therapy N =** 95	**MDMA**-AT N = 99	**Placebo + Therapy N =** 95
Medication Session 1				
Predose (overall baseline), n	**99**	**95**	**99**	**95**
Mean (SD)	125.3 (16.62)	120.7 (13.76)	79.9 (10.69)	79.6 (9.44)
Median (min, max)	122.0 (90, 180)	120.0 (92, 151)	82.0 (51, 103)	80.0 (50, 103)
Interim[a], n	**99**	**95**	**99**	**95**
Mean (SD)	138.1 (17.30)	120.4 (13.87)	85.9 (10.00)	77.5 (10.27)
Median (min, max)	135.0 (100, 191)	118.0 (94, 168)	86.0 (65, 110)	77.0 (50, 109)
Change from predose, n	**99**	**95**	**99**	**95**
Mean (SD)	12.8 (14.52)	-0.3 (10.67)	6.0 (9.36)	-2.1 (8.77)
Median (min, max)	12.0 (-24, 50)	1.0 (-23, 30)	5.0 (-16, 34)	-1.0 (-29, 16)
End of session, n	**99**	**94**	**99**	**94**
Mean (SD)	127.3 (15.55)	118.9 (14.10)	80.6 (9.38)	77.8 (10.07)
Median (min, max)	125.0 (89, 168)	118.0 (92, 164)	81.0 (54, 102)	79.0 (52, 103)
Change from predose, n	**99**	**94**	**99**	**94**
Mean (SD)	2.0 (14.45)	-1.8 (11.29)	0.7 (8.52)	-2.0 (8.82)
Median (min, max)	2.0 (-47, 53)	-2.0 (-25, 25)	0.0 (-24, 32)	-2.0 (-28, 36)
Medication Session 2				
Predose, n	**96**	**87**	**96**	**87**
Mean (SD)	126.4 (12.82)	118.5 (14.73)	81.9 (9.47)	77.3 (10.37)
Median (min, max)	127.0 (94, 158)	116.0 (83, 156)	82.0 (56, 100)	77.0 (50, 104)
Interim[a], n	**96**	**87**	**96**	**87**
Mean (SD)	144.6 (16.97)	120.0 (15.41)	88.9 (10.18)	78.8 (11.61)
Median (min, max)	145.5 (107, 185)	120.0 (85, 166)	89.5 (66, 116)	79.0 (48, 115)
Change from predose, n	**96**	**87**	**96**	**87**
Mean (SD)	18.2 (14.89)	1.5 (11.70)	7.0 (9.21)	1.5 (10.25)
Median (min, max)	18.0 (-34, 66)	0.0 (-27, 36)	6.5 (-13, 33)	0.0 (-23, 41)
End of session, n	**95**	**87**	**95**	**87**
Mean (SD)	125.7 (15.29)	117.8 (13.72)	80.9 (10.38)	76.5 (8.86)
Median (min, max)	124.0 (94, 162)	117.0 (95, 167)	81.0 (57, 108)	76.0 (56, 97)
Change from predose, n	**95**	**87**	**95**	**87**
Mean (SD)	-0.8 (12.78)	-0.7 (10.67)	-1.1 (9.28)	-0.8 (8.42)
Median (min, max)	-1.0 (-40, 28)	1.0 (-30, 22)	-1.0 (-22, 20)	-1.0 (-27, 24)

	Systolic Blood Pressure		**Diastolic** Blood Pressure	
	MDMA-AT **N =** 99	**Placebo + Therapy N =** 95	**MDMA**-AT N = 99	**Placebo + Therapy N =** 95
Medication Session 3				
Predose, n	**95**	**80**	**95**	**80**
Mean (SD)	127.2 (14.20)	118.6 (14.95)	81.9 (9.08)	77.2 (10.08)
Median (min, max)	127.0 (95, 156)	115.5 (87, 154)	84.0 (57, 109)	76.0 (56, 102)
Interim[a], n	**94**	**80**	**94**	**80**
Mean (SD)	144.4 (17.08)	118.4 (14.22)	88.0 (10.49)	76.7 (10.21)
Median (min, max)	143.0 (110, 201)	116.0 (91, 154)	89.0 (66, 115)	77.0 (52, 101)
Change from predose, n	**94**	**80**	**94**	**80**
Mean (SD)	17.1 (13.77)	-0.3 (13.53)	6.0 (9.40)	-0.5 (9.32)
Median (min, max)	16.5 (-16, 53)	-0.5 (-26, 35)	6.0 (-18, 28)	0.0 (-26, 24)
End of session, n	**95**	**80**	**95**	**79**
Mean (SD)	125.9 (15.15)	117.7 (13.36)	79.8 (9.83)	75.9 (10.17)
Median (min, max)	124.0 (99, 165)	117.5 (83, 146)	81.0 (51, 98)	77.0 (53, 101)
Change from predose, n	**95**	**80**	**95**	**79**
Mean (SD)	-1.3 (11.99)	-0.9 (11.09)	-2.1 (9.03)	-1.3 (7.91)
Median (min, max)	-2.0 (-31, 34)	0.0 (-31, 25)	-3.0 (-28, 16)	0.0 (-30, 14)

MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy
Participants are included in each medication session regardless of the dose received at that session. Includes non-missing measurements at each timepoint.
a. Prior to administration of the second part of the split dose.
Source: Table 14.6.4.2 (ISS Table 81)

Table 34: Heart Rate Results During Medication Sessions (Immediate Effect) (Pooled Phase 3; Safety Set)

	MDMA-AT **N =** 99	**Placebo + Therapy N =** 95
Medication Session 1		
Predose, n	**99**	**95**
Mean (SD)	71.7 (11.61)	73.6 (12.31)
Median (min, max)	71.0 (49, 111)	75.0 (49, 116)
Interim[a], n	**99**	**95**
Mean (SD)	83.5 (16.19)	69.5 (10.63)
Median (min, max)	81.0 (54, 128)	69.0 (48, 101)
Change from predose, n	**99**	**95**
Mean (SD)	11.8 (13.62)	-4.1 (10.19)
Median (min, max)	10.0 (-15, 48)	-4.0 (-39, 21)
End of session, n	**99**	**94**
Mean (SD)	80.9 (13.88)	72.9 (9.91)
Median (min, max)	80.0 (60, 124)	73.0 (45, 96)
Change from predose, n	**99**	**94**
Mean (SD)	9.2 (12.07)	-0.5 (12.94)

	MDMA-AT **N =** 99	**Placebo + Therapy N =** 95
Median (min, max)	8.0 (-29, 43)	1.0 (-43, 32)
Medication Session 2		
Predose, n	**96**	**87**
Mean (SD)	72.8 (10.69)	70.4 (12.66)
Median (min, max)	72.5 (52, 100)	70.0 (45, 125)
Interim[a], n	**96**	**87**
Mean (SD)	89.8 (15.34)	68.6 (11.42)
Median (min, max)	89.0 (60, 134)	68.0 (45, 98)
Change from predose, n	**96**	**87**
Mean (SD)	17.0 (12.07)	-1.7 (10.86)
Median (min, max)	16.0 (-7, 53)	-2.0 (-28, 46)
End of session, n	**95**	**87**
Mean (SD)	84.7 (14.67)	71.1 (10.16)
Median (min, max)	82.0 (57, 128)	72.0 (46, 107)
Change from predose, n	**95**	**87**
Mean (SD)	11.9 (12.80)	0.7 (8.91)
Median (min, max)	10.0 (-18, 49)	2.0 (-19, 21)
Medication Session 3		
Predose, n	**95**	**80**
Mean (SD)	73.2 (12.17)	70.1 (11.82)
Median (min, max)	72.0 (50, 105)	70.5 (43, 110)
Interim[a], n	**93**	**79**
Mean (SD)	93.3 (18.70)	67.0 (12.15)
Median (min, max)	91.0 (59, 148)	65.0 (41, 108)
Change from predose, n	**93**	**79**
Mean (SD)	20.4 (18.31)	-3.2 (9.74)
Median (min, max)	19.0 (-27, 66)	-3.0 (-37, 28)
End of session, n	**95**	**80**
Mean (SD)	84.3 (14.72)	71.5 (11.69)
Median (min, max)	84.0 (56, 124)	71.5 (45, 106)
Change from predose, n	**95**	**80**
Mean (SD)	11.1 (13.04)	1.4 (9.56)
Median (min, max)	11.0 (-20, 48)	2.0 (-22, 29)

MDMA-AT: 3,4-methylenedioxymethamphetamine-assisted therapy
a. Immediately before the second part of the split dose is administered.
Source: Table 14.6.4.2 (ISS Table 91)

11.4 Narrative Descriptions of Key Phase 2 Studies

As the Phase 2 study results were in agreement, results of only the most relevant studies (i.e., studies with the best design, power, dose, or study population to address the study question and the intended dose, indication, and patient population) are

provided as individual study results below. These include MP-8 (N = 26), MP-12 (N = 28), and MP-16 (N = 33).

Overall, MDMA was well tolerated. Available efficacy data from these Phase 2 studies suggest significant durable improvement in PTSD symptoms for at least 12 months for many participants following a complete treatment regimen of MDMA-AT.

11.4.1 MP-8

MP-8 was a randomized, triple-blinded, dose-response, Phase 2 study to assess the safety and efficacy of MDMA in veterans, firefighters, and police officers diagnosed with chronic, treatment-resistant PTSD. Participants were randomized 1:1:2 to receive a total split dose of 45 mg (30 + 15 mg; low dose), 112.5 mg (75 + 37.5 mg; medium dose), or 187.5 mg (125 + 62.5 mg; high dose) MDMA. The study consisted of a Stage 1 with 2 blinded MSs for all doses and a single open-label (OL) dose for the high dose group. Participants were unblinded individually to determine eligibility for additional OL MSs. Stage 2 consisted of crossover OL participants diagnosed with chronic, treatment-resistant PTSD of at least 6 months duration. The study consisted of an OL high dose lead-in, Stage 1, and Stage 2. Each stage consisted of 2 MSs separated by 3 to 5 weeks would receive 3 OL MSs (MS4: 150 mg [100 + 50 mg] and MS5 and MS6: 187.5 [125 mg + 62.5 mg]). All participants were to complete a LTFU visit at least 12 months after their last MS. In the original protocol, primary endpoint and unblinding occurred 1 month after MS3. The protocol was amended for the unblinding and primary endpoint to occur 1 month after MS2.

The primary efficacy endpoint was change in PTSD symptoms by Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) global scores from baseline to 1 month after MS2. Safety was assessed by AEs, SRRs, C-SSRS, vital signs, subjective units of distress (SUD), and visual analog scale (VAS) (pre-existing tinnitus, chronic pain).

A total of 26 participants were enrolled and randomized to receive either 45 mg (low dose; n = 7), 112.5 mg (medium dose; n = 7), or 187.5 mg (high dose; n = 12) MDMA during each MS.

Reductions in CAPS-IV score at the Stage 1 Primary Endpoint compared to baseline were observed overall and in each dose group, and the CAPS-IV difference score from baseline in the low dose group was significantly different from the difference score in the medium ($p = 0.002$) and high ($p = 0.022$) dose groups. At LTFU, mean CAPS-IV scores of all treated participants were significantly reduced from baseline.

MDMA was generally well tolerated. There were no deaths reported during this study. There were no TEAEs that led to premature study withdrawal. Three participants in the low dose group, 1 participant in the medium dose group, and 0 participants in the high dose group had at least 1 TEAE that led to dose reduction, interruption, or study delay. There were 2 participants in the low dose group and 1 participant in the medium dose group who reported at least 1 SAE. Of these, 1 SAE of ventricular extrasystoles was

reported during ES5 in a participant in the low dose group who crossed over to receive OL MDMA, which was evaluated by the investigator to be probably related to the IMP. This participant did not receive the second part of the split dose at this MS.

11.4.2 MP-12

MP-12 was a Phase 2 randomized, double-blinded dose ranging study examining the safety and efficacy of MDMA in participants with chronic, treatment-resistant PTSD of at least 6 months duration. Participants were randomized 9:9:5 to receive a total split dose of MDMA dose 1 of 187.5 mg (125 + 62.5 mg), dose 2 of 150 mg (100 + 50 mg), or low dose of 60 mg (40 + 20 mg). A split dose format was used, with the second part of the dose administered 1.5 to 2.5 hours after the first part. The second part of the split dose could be declined by the participant or withheld at the discretion of the clinical investigators.

The study consisted of a Stage 1 with 2 blinded (MS1, MS2) and 1 OL (MS3) MDMA MSs, and an End-of-Stage 1 follow-up; and a Stage 2 with 3 OL MSs (MS4, MS5, and MS6) and a 12-month LTFU after the last MS. In Stage 1, participants received either MDMA dose 1 of 187.5 mg (125 + 62.5 mg MDMA), MDMA dose 2 of 150 mg (100 + 50 mg MDMA), or low dose of 60 mg (40 + 20 mg MDMA). Participants who received the low dose MDMA [40 mg]) in Stage 1 had the opportunity to crossover into Stage 2 where they received 3 OL MSs 150 mg (100 + 50 mg MDMA) during the first session and 150 mg (100 + 50 mg MDMA) or 187.5 mg (125 + 62.5 mg MDMA) in the second or third sessions.

The primary efficacy endpoint was change in PTSD symptoms by CAPS-IV global scores from baseline to 1 month after MS2 (Primary Endpoint). Safety was assessed by AEs, SRRs, C-SSRS, vital signs, SUD, general wellbeing (GWB), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Paced Auditory Serial Addition Test (PASAT), and VAS (pre-existing tinnitus and chronic pain).

A total of 28 participants were enrolled and randomized to either the dose 1 group (N = 13), dose 2 group (N = 9), or low dose group (N = 6). All participants completed study termination visits.

A reduction in global CAPS-IV total severity score at the Stage 1 primary endpoint was observed in participants treated with MDMA in the study. At the Stage 1 primary endpoint, 19 (70.4%) participants had a clinically meaningful 15-point reduction in global CAPS-IV total severity score, and 11 (40.7%) participants no longer met the PTSD Diagnostic Criteria. There was a greater reduction in global CAPS-IV score from the MDMA 187.5 mg and MDMA 150 mg dose treatment groups compared to the low dose treatment groups after 2 ESs. At LTFU, mean CAPS-IV scores of all treated participants were significantly reduced from baseline. Mean CAPS-IV total scores of all treated participants declined from treatment exit to the LTFU 12-month assessment indicating the persistence of treatment effect. MDMA was generally well tolerated. There were no deaths reported during the study. There were no TEAEs that led to premature study

withdrawal. One participant in the MDMA dose 1 group and 2 participants in the MDMA dose 2 group had at least 1 TEAE that led to dose reduction, interruption, or study delay. There were 3 participants that reported an SAE (1 participant in the MDMA dose 1 group [SAE of breast cancer] and 2 participants in the MDMA dose 2 group [SAEs of tibia fracture and ovarian cyst rupture]). All SAEs resolved and were evaluated to not be related to the IMP.

11.4.3 MP-16

MP16 was an OL lead-in study, multi-site, Phase 2 study that assessed the efficacy and safety of MDMA in participants diagnosed with at least severe PTSD. Doses were 120 mg (80 + 40 mg) at MS1 and escalated to 180 mg (120 + 60 mg) at the MS2 and MS3 during the Treatment Period unless tolerability issues emerged, or it was declined by the participant. This study consisted of the following periods:

- **Screening Period:** Prospective participants were pre-screened by phone according to an IRB-approved script to ascertain if they met eligibility criteria. If deemed potentially eligible, participants received a copy of the ICF for review and were invited to the site for in-person screening which included medical assessments and a review of their medical records after consent was obtained using the IRB-approved ICF.

- **Preparatory Period (Visits 1, 2, and 4) With Enrollment Confirmation:** Participants were informed of enrollment at Visit 0. A medication tapering plan was discussed with the participant, as applicable. Within 12 days of Visit 0, the Preparatory Period began. Participants underwent 3 Preparatory Sessions (~90 minutes) with the therapy team prior to MS1. The Preparatory Period included a Baseline CAPS-5 assessment (Visit 3) assessed by an IR. These sessions helped the participant prepare for MDMA by establishing rapport with the therapist and promoting a safe set and setting for confronting trauma-related memories, emotions, and thoughts.

- **Treatment Period:** The Treatment Period occurred over a duration of 9 to 15 weeks (Visits 5 to 18) where participants completed 3 treatments consisting of an MS, followed the morning after by an Integrative Session, phone follow-ups over the next week, a second Integrative Session within 2 weeks, and a third Integrative Session within 3 to 5 weeks. The MSs were scheduled 3 to 5 weeks apart. The CAPS-5 was assessed at 2 time points during the Treatment Period (Visit 7 and Visit 12). MSs were followed by an overnight stay and a sub-study assessed feasibility of MSs without an overnight stay at select study sites.

- **Follow-up Period and Study Termination:** After the last Integrative Session (Visit 18), participants entered follow-up for approximately 4 weeks with no study visits until the final CAPS-5 assessment was given at Visit 19 (the primary outcome measure), followed by Study Termination at Visit 20. At the end of the study, the study team provided participants with an Exit Plan, which may have included referral for additional medical or therapeutic care.

The primary efficacy endpoint was to evaluate the effect of MDMA on PTSD, as measured by the estimand of change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 18 weeks post Baseline (Visit 19). Safety was assessed by AEs, AESIs, SAEs, C-SSRS, concomitant medications, and vital signs.

A total of 38 participants at 12 study sites in the US were enrolled in this study and 32 participants completed the primary endpoint as planned. One participant chose to discontinue treatment after MS2 due to an AE of increased nightmares. There was 1 SAE of attempted suicide which was not related to the IMP. No deaths occurred in this study.

Overall, MDMA doses of 120 mg to 180 mg in a controlled setting were well-tolerated and effective in reducing PTSD symptoms in participants with severe PTSD. The safety profile of MDMA did not appear to be clinically significantly different between the overnight stay group and the no overnight stay group.

11.5 Additional Results in Healthy Volunteers

11.5.1 Supplemental Phase 1 Blood Pressure and Heart Rate Results: Study MPKF

Table 35 and Table 36 summarize mean changes from predose SBP, DBP, and HR in the fed and fasted groups in this study in healthy volunteers after single doses of 120 mg. Measurements were done up to 72 hours after dosing; the results up to 24 hours are summarized in this table.

Table 35: MPKF Mean (SD) Change in Systolic and Diastolic Blood Pressure from Baseline to Visits by Treatment (Safety Analysis Set)

Visit	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)	
Timepoint Statistic	Fed N = 14	Fasted N = 16	Fed N = 14	Fasted N = 16
Visit 1.1 and 3.1				
Baseline, n	14	16	14	16
Mean (SD)	112.79 (10.786)	111.69 (10.345)	72.21 (5.964)	70.31 (8.592)
Median (min, max)	108.50 (103.00, 139.00)	110.00 (98.00, 137.00)	71.00 (64.00, 84.00)	69.50 (55.00, 88.00)
Change from baseline Visit 1.1 and 3.1				
+30 min, n	14	16	14	16
Mean (SD)	4.43 (9.428)	7.31 (5.896)	-2.71 (5.967)	2.75 (5.825)
Median (min, max)	3.00 (-10.00, 21.00)	8.00 (-4.00, 17.00)	-3.50 (-13.00, 12.00)	4.00 (-12.00, 11.00)
+1 hour, n	14	16	14	16
Mean (SD)	7.36 (13.948)	19.06 (10.951)	2.36 (8.224)	8.63 (7.500)

Visit	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)	
Timepoint Statistic	Fed N = 14	Fasted N = 16	Fed N = 14	Fasted N = 16
Median (min, max)	2.00 (-8.00, 37.00)	22.50 (1.00, 41.00)	2.00 (-8.00, 23.00)	9.50 (-5.00, 19.00)
+2 hours, n	14	16	14	16
Mean (SD)	13.29 (13.914)	19.19 (10.041)	4.79 (5.522)	8.25 (7.962)
Median (min, max)	12.50 (-10.00, 34.00)	16.00 (1.00, 35.00)	5.00 (-10.00, 12.00)	9.50 (-4.00, 25.00)
+4 hours, n	14	16	14	16
Mean (SD)	14.21 (11.510)	11.75 (7.672)	7.00 (7.981)	4.31 (6.247)
Median (min, max)	13.50 (-6.00, 38.00)	11.00 (0.00, 27.00)	6.50 (-6.00, 23.00)	4.50 (-5.00, 15.00)
+6 hours, n	14	16	14	16
Mean (SD)	11.29 (10.261)	4.88 (7.023)	2.79 (5.925)	2.44 (6.110)
Median (min, max)	9.00 (-4.00, 31.00)	1.50 (-4.00, 20.00)	4.00 (-10.00, 12.00)	3.00 (-11.00, 15.00)
+8 hours, n	14	16	14	16
Mean (SD)	4.64 (11.758)	3.00 (7.294)	0.93 (7.216)	1.25 (5.927)
Median (min, max)	1.50 (-13.00, 31.00)	2.00 (-13.00, 19.00)	1.00 (-15.00, 14.00)	1.00 (-10.00, 15.00)
+12 hours, n	14	16	14	16
Mean (SD)	2.43 (12.593)	2.56 (8.687)	0.36 (9.803)	1.19 (6.442)
Median (min, max)	5.00 (-20.00, 20.00)	1.00 (-9.00, 23.00)	-1.50 (-11.00, 29.00)	1.00 (-8.00, 14.00)
+24 hours, n	14	16	14	16
Mean (SD)	-6.36 (8.427)	-1.44 (6.928)	-3.07 (5.744)	-0.44 (6.261)
Median (min, max)	-6.00 (-20.00, 7.00)	-1.00 (-12.00, 12.00)	-1.50 (-13.00, 7.00)	0.00 (-12.00, 8.00)

N: number of participants in the Analysis Population; n: number of participants with non-missing data in the category.
Notes: Baseline is defined as the last assessment taken on Day 1 pre-dose.
Only 14 of the 16 participants completed the fed treatment.
Table presents nominal times.
Source: MPKF CSR, Table 14.3.5.1 and Listing 16.2.8.2.

Table 36: MPKF Mean (SD) Change in Heart Rate from Baseline to Visits by Treatment (Safety Analysis Set)

Visit Timepoint Statistic	Heart Rate (bpm) Fed N = 14	 Fasted N = 16
Visit 1.1 and 3.1		
Baseline, n	14	16
Mean (SD)	63.86 (6.949)	59.88 (7.210)
Median (min, max)	62.00 (53.00, 80.00)	60.00 (49.00, 74.00)
Change from baseline Visit 1.1 and 3.1		
+30 min, n	14	16
Mean (SD)	5.86 (6.792)	2.75 (9.504)
Median (min, max)	6.00 (-3.00, 19.00)	0.00 (-9.00, 30.00)
+1 hour, n	14	16
Mean (SD)	11.79 (6.897)	16.69 (15.252)
Median (min, max)	9.50 (4.00, 27.00)	13.00 (-2.00, 53.00)
+2 hours, n	14	16
Mean (SD)	19.14 (12.240)	19.75 (17.063)
Median (min, max)	17.00 (5.00, 45.00)	15.50 (-1.00, 54.00)
+4 hours, n	14	16
Mean (SD)	15.93 (8.241)	14.88 (8.277)
Median (min, max)	15.50 (5.00, 33.00)	15.00 (0.00, 32.00)
+6 hours, n	14	16
Mean (SD)	9.71 (8.801)	12.63 (11.206)
Median (min, max)	9.00 (-5.00, 30.00)	12.50 (-10.00, 34.00)
+8 hours, n	14	16
Mean (SD)	8.21 (7.728)	10.13 (9.804)
Median (min, max)	8.50 (-2.00, 22.00)	10.00 (-10.00, 27.00)
+12 hours, n	14	16
Mean (SD)	6.00 (6.251)	8.06 (8.645)

Visit Timepoint Statistic	Heart Rate (bpm) Fed N = 14	 Fasted N = 16
Median (min, max)	6.00 (-5.00, 15.00)	10.00 (-6.00, 24.00)
+24 hours, n	14	16
Mean (SD)	1.93 (6.956)	9.00 (10.912)
Median (min, max)	2.50 (-8.00, 13.00)	9.00 (-8.00, 32.00)

bpm: beats per minute; N: number of participants in the Analysis Population; n: number of participants with non-missing data in the category.
Notes: Baseline is defined as the last assessment taken on Day 1 predose.
Only 14 of the 16 participants completed the fed treatment.
Table presents nominal times.
Source: MPKF CSR, Table 14.3.5.1 and Listing 16.2.8.2.