Investigator's Brochure

SPONSOR	Multidisciplinary Association for Psychedelic Studies (MAPS)
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List of Abbreviations

Ach	Acetylcholine
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
ARF	Acute Renal Failure
AVP	Arginine Vasopressin
BDI	Beck Depression Inventory
BDI-II	Beck Depression Inventory II
BDNF	Brain Derived Neurotrophic Factor
BOLD	Blood Oxygen Level Dependent
C	Celsius
CAPS	Clinician Administered PTSD Scale
CBF	Cerebral Blood Flow
cGMP	Current Good Manufacturing Practice
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
C-SSRS	Columbia Suicide Severity Rating Scale
CTproAVP	Stimulating Secretion of Copeptin
DAT	Dopamine Transporters
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DIC	Disseminated Intravascular Coagulation
DMF	Drug Master File
DNA	Deoxyribonucleic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
E	Embryonic Days
EEG	Electroencephalography
EKG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
G-CSF	Granulocyte-colony Stimulating Factor
GD	Gestational Days
HHMA	3,4-Dihydroxymethamphetamine
HMA	4-Hydroxy-3-methoxy-amphetamine
HMMA	4-Hydroxy-3-methoxy-methamphetamine
HPA	Hypothalamus-pituitary-adrenal
HR	Heart Rate
IB	Investigator's Brochure
IL	Interleukin
IND	Investigational New Drug
LD50	Lethal Dose in 50% of Cases
LSD	d-Lysergic Acid Diethylamide
MAA-1	Phase 2 clinical trial of MDMA-assisted therapy for social anxiety in people on the autism spectrum
MAO	Monoamine Oxidase
MAO-A	Monoamine Oxidase A
MAOI	Monoamine Oxidase Inhibitor

MAPS	Multidisciplinary Association for Psychedelic Studies
MDA	3,4-Methylenedioxyamphetamine
MDA-1	Phase 2 clinical trial of MDMA-assisted psychotherapy for anxiety in relation to a life-threatening illness
MDE	Methylenedioxyethylamphetamine
MDMA	3,4-Methylenedioxymethamphetamine
MP-1	Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Charleston, South Carolina
MP1-E2	Relapse study Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Charleston, South Carolina
MP-2	Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Switzerland
MP-3	Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Israel
MP-4	Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Canada
MP-8	Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Canada
MP-9	Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Canada
MP-12	Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Canada
MP16	Open-label Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in USA
MP17	Open-label Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD in Canada
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MT-1	Phase 1 clinical trial of MDMA-assisted psychotherapy for PTSD in healthy volunteers in Charleston, South Carolina
NET	Norepinephrine Transporter
NK	Natural Killer
NLP	Natural Language Processing
PASAT	Paced Auditory Serial Addition Task
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PMA	Paramethoxyamphetamine
PMMA	Paramethoxymethamphetamine
PND	Postnatal Day
PTSD	Posttraumatic Stress Disorder
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
*r*CBF	Regional Cerebral Blood Flow
SAE(s)	Serious Adverse Event(s)
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SERT	Serotonin Transporter
SIADH	Syndrome of Inappropriate Antidiuretic-hormone Secretion
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SPECT	Single Photon Emission Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TNF-α	Tumor Necrosis Factor-alpha
VHD	Valvular Heart Disease
VMAT2	Vesicular Monoamine Transporter 2
WBC	White Blood Cell Count
8-OH-DPAT	8-Hydroxy-2-(di-n-propylamino)tetralin

1.0 Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a United States (U.S.)-based non-profit research and educational organization supporting research of the therapeutic potential of 3,4-methylenedioxymethamphetamine (MDMA). MAPS is sponsoring clinical trials of MDMA-assisted psychotherapy for patients with chronic disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety associated with autism, and anxiety related to terminal illnesses. MDMA-assisted psychotherapy is an experimental treatment that combines psychotherapeutic techniques with administration of MDMA, a pharmacological adjunct that enhances aspects of psychotherapy. Prior to placement on the Drug Enforcement Administration's (DEA) list of Schedule I substances, MDMA was administered to thousands of people in psychotherapeutic practice outside of clinical trials. According to the 2011 United Nations World Drug Report, 11 to 28 million people aged 15 to 64 used Ecstasy, material represented as containing MDMA, around the world in various non-medical settings [1-5]. The information presented in this Investigator's Brochure (IB) is summarized from published research studies of MDMA conducted by groups outside of the sponsor, sponsor collected data and published studies of Ecstasy use. For the purposes of this document MDMA will be used to refer to drug of known purity used in a controlled setting and Ecstasy will be used to describe drug-related information gathered from epidemiological settings.

MDMA is a ring-substituted phenethylamine also known as methylenedioxymethamphetamine. MDMA is structurally similar, but functionally distinct, from amphetamines. MDMA is a chiral molecule, the sponsor uses racemic MDMA in the form of white crystalline powder compounded with inert material into capsules. The hydrochloride salt of MDMA is readily water soluble and is lipophilic once ionized. A substantial amount of data, both clinical and nonclinical, has been collected for over half a century of research on the physiological and psychological effects of MDMA in humans and animals. Estimates from animal data suggest a median lethal dose (LD50) in humans between 10 to 20 mg/kg [6]. Due to a wide range of responses to identical milligram per kilogram (mg/kg) dosing [7], the sponsor's human trials use fixed doses equivalent to between 1 and 4 mg/kg (active doses in studies range from 75 mg to 225 mg). Onset of MDMA effects occurs 30 to 60 minutes after oral administration [8, 9`], peak effects appear 75 to 120 minutes post-drug [7, 10-12], and duration of effects lasts from 3 to 6 hours [10, 11, 13], with most effects returning to baseline or near-baseline levels 6 hours after drug administration. The elimination half-life of active doses of MDMA is 8 to 9 hours [14].

The pharmacokinetics of MDMA in humans has been characterized using oral doses of up to 150 mg MDMA. MDMA disposition in the body follows nonlinear pharmacokinetics. As described in Figure 1 (see Section 5.2.1 Pharmacokinetics), metabolism of MDMA results in *N*-demethylation to 3,4-methylenedioxyamphetamine (MDA). The parent compound and MDA are further *O*-demethylated to 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. Both HHMA and HHA are subsequently *O*-methylated mainly to 4-hydroxy-3-methoxy-methamphetamine (HMMA) and 4-hydroxy-3-methoxy-amphetamine (HMA). These four metabolites, particularly HMMA and HMA, are known to be excreted in the urine as conjugated glucuronide or sulfate metabolites [14].

MDMA is a triple monoamine reuptake inhibitor, and similar drugs in this class have been found to exert potent anti-depressant activity with a favorable safety profile in clinical trials [15, 16]. MDMA concomitantly promotes release, inhibits reuptake, and extends duration of serotonin, norepinephrine, and dopamine in the synaptic cleft to increase serotonergic, noradrenergic, and dopaminergic neurotransmission. MDMA has self-limiting subjective and physiological effects due to inhibitory activity on tryptophan hydroxylase [17-19], which prevents additional serotonin from being produced and released. This inhibition is reversible [20]. MDMA produces anxiolytic

and prosocial effects through release of the monoaminergic neurotransmitters, with the greatest effect on serotonin, followed by norepinephrine and dopamine [21-25]. MDMA has been shown to acutely decrease activity in the left amygdala and increase blood flow to the prefrontal cortex (PFC) in the brain [26-28]. MDMA has also been found to increase serum levels of the neurohormones oxytocin and arginine vasopressin (AVP) in humans [19, 29-35]. Some studies in healthy volunteers suggest that MDMA increases trust and attenuates reactivity to threatening cues, which are at least partially associated with oxytocin release [29, 36-38]. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, and make unpleasant memories less disturbing while enhancing communication and capacity for introspection [39-42]. These factors taken together can provide the opportunity for a corrective emotional experience in the context of psychotherapy. Many of the therapeutic effects of MDMA-assisted psychotherapy are evident within a short period of treatment, often after the initial session.

Increased feelings of interpersonal closeness, changes in social perception and reduced anxiety may make MDMA a suitable pharmacological adjunct to enhance psychotherapy for anxiety disorders, such as PTSD and social anxiety in autistic adults. MDMA may provide a much-needed option in the treatment of PTSD and anxiety associated with other conditions. Published results from MAPS study (MP-1) showed clinically and statistically significant improvements in PTSD severity in 20 per protocol subjects [43]. Findings from the long-term follow-up of MP-1 suggest that therapeutic benefits were sustained for an average of 41 months post-treatment [44]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) demonstrated clinically significant improvements in PTSD symptoms, with results in the 125 mg MDMA dose group numerically but not statistically superior to the 25 mg MDMA dose group [45]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. There were no possibly or probably drug-related Serious Adverse Reactions (SARs) or safety concerns in either study. Subsequently, safety findings from initial studies were confirmed in five Phase 2 PTSD studies, including one dose response study in military veterans, firefighters and police officers (N=26, MP-8) [46], another dose response study employing multiple therapist teams with trauma from any cause (N=28, MP-12) [47], an active-controlled study conducted in Israel (N=10, MP-9), a placebo-controlled study conducted in Canada (N=6, MP-4), and an open-label Phase 1/Phase 2 pilot study of a combination of MDMA-assisted psychotherapy with a form of conjoint cognitive behavioral therapy geared toward dyads is now complete (N=12, MPVA-1)[48]. Safety findings appear generalizable to other indications, as demonstrated in a Phase 2 social anxiety study in autistic adults (N=12, MAA-1) [49, 50], and a Phase 2 anxiety study in participants with a life-threatening illness (N=21, MDA-1).

Data from MAPS studies and published literature show that MDMA produces sympathomimetic effects that include significant transient, self-limiting increases in heart rate (HR) and blood pressure that are likely to be well tolerated by healthy individuals [7, 9-11, 26, 51-53]. Most people do not experience elevations that exceed those seen after moderate exercise. These results were reproduced in an investigator-sponsored Phase 1 safety study [54]. Risks posed by elevated blood pressure are addressed by excluding candidates with a history of cardiovascular, cerebrovascular disease, or with pre-existing uncontrolled hypertension and by regularly monitoring blood pressure and pulse throughout experimental sessions. Common reactions reported in the literature and clinical trials from MDMA are transient and diminish as drug effects wane during the session and over the next one to 7 days. MDMA may reduce responsiveness to changes in water/salt balance after normal and increased water consumption [55]. The effects include lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, headache, impaired gait or balance, muscle tension, ruminations, feeling cold, and thirst (see Section 5.3.9 Adverse Events). MDMA is also a mild immunosuppressant [56]. Due to their limited duration, these sub-acute reactions are not likely to have clinical significance.

As of October 1, 2018, 1570 individuals exposed to MDMA in controlled research settings (which includes 267 participants in MAPS-sponsored Phase 1 and Phase 2 studies), there have been no unexpected SARs to date and expected SARs have been rare and non-life threatening. As of May 31, 2019, a single expected SAR (increased ventricular extrasystoles), has been reported in MAPS-sponsored clinical trials.

There have been a number of serious incidents among individuals who use Ecstasy (material represented as containing MDMA, as defined above) around the world in various non-medical settings [1-5]. These include fatalities reported after Ecstasy and poly-drug use in unsupervised and uncontrolled settings. These events are relatively rare given the prevalence of Ecstasy use, estimated to be in the millions worldwide [57, 58]. The most common adverse effects in Ecstasy and poly-drug use include hyperthermia, psychiatric problems, hepatotoxicity, and hyponatremia [59-63] (see Section 4.4 Toxicology in Animals and Epidemiological Settings and 4.5 Serious Reports, Mortality, and Morbidity in Animals and Epidemiological Settings).

2.0 Introduction

MDMA is not a novel compound. The history of its use in humans predates controlled studies in healthy volunteers and clinical trials. MDMA was first synthesized and patented by Merck in 1912 [64] and is currently not covered by a patent. MAPS holds the Drug Master File (DMF) and an Investigational New Drug (IND) file for MDMA with the U.S. Food and Drug Administration (FDA). After MDMA was rediscovered by the chemist Alexander Shulgin in 1976 [65], he and his colleagues provided initial reports of its pharmacology, with 80 mg to 160 mg MDMA required to produce desired subjective effects in humans [66, 67]. MDMA was found to robustly influence human emotional status in a unique way [67] without adversely effecting physiological functions or perception, such as visual perception or cognition [8, 10, 12, 13].

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor, with additional effects on limiting neurotransmitter production and degradation. Its prominent effects on serotonin differentiate it from amphetamine and methamphetamine, which primarily act to increase catecholamines such as norepinephrine and dopamine [21, 68]. In the Merck Index, MDMA resides in the Entactogen class [69]. Entactogens contain a ring-substituted amphetamine core, belong to the phenethylamine class of psychoactive drugs, and are described as promoting acceptance and compassion for self and others, changing recognition and response to emotions, and increased interpersonal closeness [19, 40, 70, 71]. In comparison to anxiolytics, antidepressants and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to psychotherapy. Two to six administrations of MDMA, spaced approximately 1 month apart at active doses of 75 mg to 125 mg, may be an alternative to other medications that require daily dosing. This infrequent dosing regimen mitigates adverse event (AE) frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over daily dose medications.

Shulgin and Nichols were the first to report the effects of MDMA in humans [67]. MDMA-assisted psychotherapy first occurred during the mid-to-late 1970s after Shulgin introduced MDMA to a psychotherapist, Leo Zeff. Reported effects of MDMA include enhanced feelings of closeness to others, wellbeing, and insightfulness [72-74]. Prior to placement in Schedule I, MDMA was used in psychotherapy for individuals, couples, and groups to treat various psychological disorders, including moderate depression and anxiety [73, 75-77]. It was also found to be useful in reducing physical pain secondary to certain kinds of cancer [76]. No formal controlled clinical trials of safety and efficacy were conducted at the time [73, 78].

During the early 1980s, increasing numbers of people began using MDMA, sold as "Ecstasy" outside of therapeutic contexts [1]. The first wave of non-medical use occurred not only in dance clubs, but also in groups of people who used the drug in a self-exploratory or spiritual context. Non-medical use continues today in the same contexts [4, 79]. In the U.S., an estimated 800,000 people reported initiating Ecstasy use in the past year [80], and approximately 2.1 million Europeans between the ages of 15 and 64, or approximately 0.6% of the population, reported using Ecstasy in 2013 [81].

MDMA was added to the list of Schedule I controlled substances in the U.S. in 1985, defining it as a drug with a high potential for abuse and no accepted medical use [82, 83]. Classification as a Schedule I controlled substance, combined with the early research in animals and recreational users, hampered clinical research into the medical uses of MDMA until the 1990s. Shortly after it was scheduled, animal studies described long-term decreases in markers of serotonergic functioning after high or repeated doses of MDMA administration [84], however these were not relevant to doses in clinical trials [85, 86]. A recently published meta-analysis took careful steps to overcome methodological limitations in previous work, and found only modest indicators of long-term impairment in cognitive function in humans [61]. A systematic review of brain imaging studies in moderate ecstasy users found no convincing evidence for structural or functional changes [87]. Reports of AEs, such as hyperthermia, following Ecstasy use [88-90] and studies in Ecstasy users reporting changes in serotonin transporter (SERT) density, impaired memory and executive function raised concerns regarding the safety of MDMA administration [91-95]. However uncontrolled studies of Ecstasy use and nonclinical animal studies that use inappropriately high doses of MDMA produce findings that are open to several interpretations [86, 96]. The vast majority of publications of Ecstasy users are retrospective reports in polydrug-users [61, 97].

While the initial studies in the 1990s conducted in humans examined the physiological effects of MDMA strictly from a safety perspective, current investigations have examined the effects on attention, prosocial effects, memory and brain activity, and human drug discrimination. Findings from an initial sponsor-funded study indicated that MDMA-assisted psychotherapy could be conducted safely in people with chronic PTSD who had failed first line treatments [98]. This was repeated in a chronic, treatment-resistant PTSD sample in a sponsor-supported study (MP-1) [44] which demonstrated durable improvement in PTSD severity, with no difference in cognitive function between placebo and MDMA groups after an active dose of MDMA was given on two occasions, spaced 1 month apart. In addition, placebo-controlled Phase 1 clinical trials confirmed that MDMA produces an easily controlled intoxication characterized by euphoria, increased well-being, sociability, self-confidence, extroversion, transient increases in anxiety, and minor alterations in perception [8, 10-12, 29, 30, 37, 99, 100].

MAPS has completed six Phase 2 investigations of MDMA-assisted psychotherapy for treatment of PTSD (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12), and one extension study for relapse of PTSD (MP1-E2). Published reports support symptom reduction with a single SAR [47, 101, 102]. The pooled Phase 2 efficacy results in PTSD participants indicate that MDMA-assisted psychotherapy administered in a controlled clinical setting demonstrates a substantial improvement to safety, efficacy, and compliance over approved treatments for patients with moderate to severe PTSD [44, 45]. Significant durable improvement in PTSD symptoms lasted for at least 12 months for many participants after MDMA-assisted psychotherapy in completed studies. A pilot study of a combination of MDMA-assisted psychotherapy with a form of conjoint cognitive behavioral therapy geared toward dyads is now complete (MPVA-1) [48], and two open-label Phase 2 PTSD studies testing the same dosing regimen as Phase 3 trials are near completion (MP16 and MP17). These Phase 2 clinical studies in subjects with PTSD supported the initiation of Phase 3 clinical studies for treatment of PTSD with MDMA-assisted

psychotherapy sponsored by MAPS [103]. MAPS completed an End of Phase 2 Meeting with FDA for MDMA-assisted psychotherapy for treatment of PTSD on November 29, 2016. On August 15, 2017, the FDA granted Breakthrough Therapy Designation to MDMA for the treatment of PTSD. The first of two Phase 3 MDMA-assisted psychotherapy trials commenced in November 2018 at approximately fifteen study sites in the U.S., Canada, and Israel. Both Phase 3 trials will have a planned sample size of 100 participants with severe PTSD and a randomized, double-blind, placebo-controlled design. In light of the favorable risk/benefit profile of MDMA, the pivotal efficacy and safety results from these Phase 3 trials are likely to form the basis of a marketing authorization application for the use of MDMA as an adjunct to supportive psychotherapy.

Additional MDMA research studies supported by the sponsor include a randomized, placebo-controlled, double-blind study of the effects of 100 mg MDMA on startle response in 30 healthy volunteers which has enrolled eight participants by 1 October 2018. This study continues to recruit participants.

Based on clinical experience with PTSD, MAPS is exploring additional indications for this treatment. Two studies have been completed exploring the use of MDMA-assisted therapy for social anxiety in autistic adults (MAA-1) and MDMA-assisted psychotherapy to address anxiety associated with a life-threatening illness (MDA-1).

This IB will present available nonclinical and clinical data on MDMA, as well as epidemiological studies in Ecstasy users published through 1 May 2019. Available AE data is presented based on pooled data from the six Phase 2 studies and by individual studies of other indications or open-label trials. No updates to the risk/benefit profile have been found since the last edition of this IB.

3.0 Physical, Chemical, and Pharmaceutical Properties and Formulation

MDMA is structurally similar, but functionally distinct, from amphetamines and mescaline. MDMA, also known as 3,4-methylenedioxy-N-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula of $C_{11}H_{15}NO_2$. It was first synthesized as a precursor of a haemostatic drug called methyl hydrastinine as a phenylisopropylamine derivative of safrole, an aromatic oil found in sassafras, nutmeg, and other plants [6].

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [6, 104]. Research in humans to date and the majority of nonclinical studies have used racemic MDMA, or an admixture containing equal amounts of both enantiomers. Studies of drug discrimination in rodents [105, 106] and studies of self-administered and experimenter-administered MDMA enantiomers in primates [23, 107-110] suggest that MDMA enantiomers may produce different physiological and rewarding effects, and there may be some synergy between the two when administered as a racemate. It seems that R (-)-MDMA may have hallucinogen-like effects, compared to S (+)-MDMA, which exhibits psychomotor stimulant-like effects. Findings comparing the effects of the enantiomers of the related compound methylenedioxymethamphetamine [111] may occur in humans. According to an *in vivo* microdialysis study in rodents, S(+)-MDMA may be associated with greater dopamine release in specific brain areas [112]. A study conducted in 2014 in monkeys found that found that S(+)-MDMA, but not R(-)-MDMA, significantly increased extracellular dopamine levels in the dorsal striatum, whereas S(+)-MDMA significantly increased serotonin levels [23]. S([23]. *In vitro* studies reported greater binding at a specific alpha nicotinic acetylcholine (Ach[113]. MDMA available for humans in clinical trials is racemic, containing roughly equal amounts of both enantiomers. Any differential effects of the enantiomers remain untested in humans. The

sponsor will use racemic MDMA in all current and planned studies. Unless otherwise stated, MDMA is used throughout this document to refer to the racemic mixture.

For clinical trials, the sponsor uses the racemic anhydrous hydrochloride salt of MDMA. Since this is the formulation used in all prior investigations in humans, the sponsor will continue to use the hydrochloride salt of MDMA. The hydrochloride salt of MDMA is readily water soluble with a pK_a of 9.9 [114], which influences whether it is ionized in plasma and slightly reduces its ability to cross into oral fluid. MDMA is also more lipophilic, which drives it into oral fluid, and may influence its ability to pass the blood brain barrier and influence signaling in the central nervous system (CNS) [115].

Sponsor-supported early Phase 1 and 2 studies in the U.S. used MDMA manufactured in 1985 by David Nichols, Ph.D., at the Department of Medicinal Chemistry and Pharmacology, Purdue University, West Lafayette, IN. The MDMA was manufactured as a single lot for use in FDA-regulated clinical trials. A stability analysis conducted in 2006 indicates that the compound remains highly stable and pure after 21 years of storage [116]. Studies conducted outside of the U.S. use MDMA from a single batch manufactured in 1998 by Lipomed AG in Arlesheim, Switzerland. The most recent analysis of drug stability and purity conducted on February 2, 2010 confirmed that this MDMA is 99.9% pure with no detectable decomposition. As of November 2018, the sponsor has released a new lot of Investigational Medicinal Product (IMP) manufactured according to current Good Manufacturing Practices (cGMP), and all subsequent sponsor-supported studies will follow this standard globally. The drug substance manufacturer is Onyx Scientific, Ltd in the United Kingdom and the drug product manufacturer is Sharp Clinical Services in the U.S. For sponsor-supported studies, MDMA in the form of white crystalline powder is compounded with inert material into capsules. Capsules are administered orally with a glass of water.

MDMA doses in sponsor-supported early Phase 1 and 2 studies are fixed within the therapeutic dose range of 75 mg -125 mg, rather than based on body weight, based on epidemiological information and lack of linear dose response with behavioral effects in Phase 1 and sponsor-supported studies [7]. The clinical dose tested in Phase 3 trials is a flexible dose ranging from 80 mg to 120 mg, which is equivalent to 1.1 mg/kg to 1.8 mg/kg in the initial dose for a 70 kg person. The supplemental half-dose of 40 mg to 60 mg is equivalent to 0.89 mg/kg. Various comparator and active doses of MDMA are also being tested in the clinical trials.

Although MDMA does not require special conditions for storage, temperature will be monitored. The drug product is stored in sealable containers placed within a dark safe at ambient temperature. MDMA is a Schedule I controlled substance and is stored and handled in compliance with relevant federal, state, and local regulations. In accordance with the requirements of the U.S. DEA and international drug regulatory authorities, license holders will be responsible for storing and dispensing the MDMA, and ensuring it is stored under appropriate protections.

Inactive excipients are intended to maintain the blind by creating capsules of equal weight. Lactose has been used in Phase 2 as an inactive material of similar appearance and was selected because it can be safely consumed by most people and is inactive. Whenever conducting blinded studies, the sponsor will continue to employ lactose or inactive materials that exist as white powders without significant odor that can be safely administered in humans. The purpose of this excipient is solely to permit placebo or active placebo administration under blinded conditions.

4.0 Nonclinical Studies

Findings from nonclinical animal research, retrospective studies of Ecstasy use and case reports of Ecstasy use in humans are presented. Research into the pharmacological, physiological, or psychological effects of MDMA began in the 1950s, when the U.S. Army administered MDMA to guinea pigs, monkeys, mice, rats, and dogs as part of a military research program, possibly intending to develop chemical incapacitants or means of enhancing interrogation [117]. Investigations of the pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA that are not human-equivalent doses. Studies of MDMA have been conducted in primates and rodents. Primate species studied include baboon, macaque, rhesus monkey, and squirrel monkey, and rodents include mice and rats. Studies of circadian rhythm have occurred in hamsters [118]. Beginning in the mid-2000s onwards, reports re-examining these effects have questioned the applicability of interspecies scaling models for MDMA, and have supported nonlinear pharmacology [86, 119, 120]. In general, doses in the range of 1 to 5 mg/kg in animals are relevant to human research and are described in more detail in Section 4.2.2 Pharmacodynamics in Animals. Findings in doses above this that show a toxic effect are described when relevant in Section 4.4 Toxicology in Animals and Epidemiological Settings.

Evidence exists for intentional human use of MDMA, (Ecstasy, E, Molly and other names), as early as the late 1960s [65], and there are records of a police seizure of MDMA in the early 1970s [121]. MDMA was administered to thousands of people prior to scheduling and many continue to use Ecstasy around the world in various non-medical settings [1-5]. In this IB, "Ecstasy" (or other common names) refers to material assumed to be MDMA used in naturalistic settings (see epidemiology sections), however when used in these uncontrolled settings the drug may not contain only or any MDMA. One of the problems in assessing the effects of Ecstasy in users is determining the purity and identity of the substance. It may contain other substances along with or instead of MDMA, and when present, the amount of MDMA can vary widely [122-124]. Most studies rely on self-reported use and do not attempt to confirm that material used is MDMA. Synthesis of MDMA is relatively simple and is often produced illegally in laboratories with no quality control. These synthesized tablets also may be cut or mixed with other psychoactive substances. Substances found mixed with MDMA have included amphetamine methamphetamine, dextromethorphan, paramethoxymethamphetamine (PMMA), paramethoxyamphetamine (PMA), cathinones, ketamine, caffeine, and ephedrine [124, 125]. Retrospective studies in Ecstasy users are described in Section 4.3 Physiological Effects in Epidemiological Settings and case reports of morbidity and mortality in Ecstasy users are included in Section 4.5 Serious Reports, Mortality, and Morbidity in Animals and Epidemiological Settings to provide the context of potential safety information of a related compound to MDMA which has extensive use outside of a research setting.

4.1 Nonclinical Pharmacology

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor. Its prominent effects on serotonin differentiate it from amphetamine and methamphetamine, which primarily act on dopamine and norepinephrine [21, 68]. In the following sections, the pharmacology of MDMA is presented based on nonclinical animal studies and epidemiological studies.

4.2 Pharmacology in Animals

4.2.1 Pharmacokinetics in Animals

MDMA is metabolized via two hepatic pathways. In the major pathway in rats, MDMA is *O*-demethylated by cytochrome P450 CYP2D1 and 3A2 to form HHMA, which is *O*-methylated to generate HMMA by catechol-O-methyltransferase (COMT). In the minor pathway in rats, MDMA is *N*-demethylated by CYP1A2 and 2D1 to form MDA, which is an active metabolite. MDA is *O*-demethylated by the same enzymes as MDMA, with subsequent metabolism by COMT. Metabolites of MDMA are excreted in urine as glucuronide and sulfate conjugates. MDMA and metabolites have shorter half-lives in rats than humans at comparable doses based on plasma C_{max} values. Rats tend to form more MDA and glucuronide-conjugated metabolites than humans [126]. As MDMA dose increases above 2.5 mg/kg subcutaneous (s.c.) or intraperitoneal (i.p.) in rats, a larger percentage of the administered dose is shunted to the *N*-demethylation pathway, resulting in greatly enhanced formation of MDA [127]. Comparison of metabolic pathways between rats and mice given 10 mg/kg i.p. MDMA indicate that 49.1% of MDMA is metabolized through the HMMA pathway in mice versus 72% in rats, and 18.3% of MDMA is metabolized through the MDA pathway in mice versus 28% in rats based on AUC ratios to MDMA. MDMA at 10 mg/kg was also found to be eliminated more rapidly in mice (0.4 hours, i.p.) than rats at (1.1 hours, s.c.) [86, 128].

To address questions of the applicability of interspecies scaling models and nonlinear pharmacology of MDMA, a study examining MDMA and metabolites in rats given 2.5, 5, and 10 mg/kg s.c. found that MDMA metabolism is nonlinear in rats, with 2.5 mg/kg producing plasma C_{max} levels approximating those seen in humans receiving between 75 and 100 mg [14, 127, 129]. Injections of 2 mg/kg s.c. or i.p. in rats were found to be similar to oral administration of 100 mg MDMA in humans based on plasma MDMA and metabolite concentrations [86]. Based on plasma values, a dose of 3 mg/kg i.p. MDMA administered in mice was comparable to a single oral dose of 100 mg in humans [105]. Studies in rats and mice provide compelling evidence of nonlinear pharmacokinetics, likely due to saturation of metabolic enzymes, determined by greater than expected AUC values for MDMA and MDA after subsequent MDMA doses, while AUCs for HHMA and HMMA remained lower than expected [127, 128].

Single dose pharmacokinetics of oral 7.4 mg/kg MDMA in squirrel monkeys shows two to three-fold higher plasma MDMA concentrations than humans receiving an oral dose of 100 mg, although allometric interspecies scaling predicts an equivalent dose [119]. A study directly comparing MDMA pharmacokinetics in humans and monkeys found that the two species metabolized MDMA in a similar but not identical manner - MDMA half-life in monkeys was less than half the duration seen in humans (1.1 hours at a dose of 2.8 mg/kg in squirrel monkeys versus 8.4 hours after 1.5 mg/kg in humans). Both monkeys and humans exhibit nonlinear pharmacokinetics [14, 130, 131], and it appears they exhibit similar plasma MDMA levels after receiving the same dose of MDMA [132, 133]. These pharmacokinetic findings suggest that nearly all toxicological and behavioral preclinical studies of MDMA use overestimated doses that exceed human-equivalent doses by 2.7 to 10.7 times, depending on route of administration, due to both simple dose conversion and allometric scaling. Consequently, it is difficult to interpret the relevance of findings in preclinical studies employing these dosing regimens.

Table 1: Pharmacokinetic Constants for Plasma MDMA After Various Routes of Administration to Humans or Animals

	C_{max} (ng/ml)	AUC (h•ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	References
Rat [A]					
2 mg/kg i.p.	210±108	163±56	0.14±0.08	0.80±0.16	[86]
2 mg/kg s.c.	196±50	304±65	0.75±0.29	0.79±0.14	[86]
2 mg/kg p.o.	46±15	61±42	0.56±0.31	0.77±0.11	[86]
2.5 mg/kg s.c.	164.1±47.1	272.1±71.6	0.6±0.2	1.1±0.9	[127]
5 mg/kg s.c.	370.8±41	879.1±133.2	0.9±0.6	0.9±0.1	[127]
10 mg/kg s.c.	893.9±90.7	2879.9±491.5	1.1±0.4	2±0.6	[127]
Mouse [B]					
3 mg/kg i.p.[C]	369.8	---	0.17	0.6	[105]
10 mg/kg i.p.	1109±87	1233±53	≤0.3	0.4	[128]
20 mg/kg i.p.	2152±82	2611±86	≤0.3	0.6	[128]
Squirrel Monkey					
1.4 mg/kg p.o.	100.2±51.5	340.3±248.4	1±0.4	1.8±0.9	[134]
2.8 mg/kg p.o.	312.7±92.8	1314.2±581.5	1.1±0.4	2.1±0.8	[134]
5.7 mg/kg p.o.	723.6±228	3866.2±891	1.3±0.9	2.6±0.7	[134]
10 mg/kg p.o.	1594.5±295.6	12,839.2±2144.6	1.3±0.9	4.2±1.5	[134]
7.4 mg/kg s.c.	1227±167	5006±528	---	3.5±0.9	[119]
7.4 mg/kg p.o.	773±157	3408±821	---	3.1±0.5	[119]
Human					
1.0 mg/kg p.o.	147±10	1389±119	2.3±0.2	7.2±0.6	[135]
1.6 mg/kg p.o.	292±76	3485±760	2.4±0.6	8.1±2.1	[129]
1.6 mg/kg p.o.	254.7±60.4	3070.6±673.4	2.4±0.6	8.4±1.6	[132]
2.0 mg/kg p.o.	442-487	5133-5232	1.5-2.0	6.9-7.2	[14]

[A] *Male Sprague-Dawley rats*
[B] *Male FVB mice*
[C] *Fantegrossi et al. reported mean pharmacokinetic parameters of R(-)-MDMA and S(+)-MDMA after administering racemic MDMA. In this table, plasma racemic C_{max} values estimated by taking sum of R(-) and S(+), while T_{max} and $t_{1/2}$ presented as an average of the enantiomers' values.*
[D] *All values were above levels of detectability.*

4.2.2 Pharmacodynamics in Animals

Most effects of MDMA likely arise directly from monoamine reuptake inhibition and release, and indirectly from activation of downstream monoamine receptors and subsequent secretion of neuromodulators oxytocin and AVP. MDMA binds primarily to membrane-bound monoamine transporters, which remove monoaminergic neurotransmitters from the space between neurons, known as the synaptic cleft. MDMA appears to alter the conformation of the transporters, enabling monoamines to diffuse out of the neuron rather than being actively transported into the presynaptic neuron [68, 136-138]. MDMA prevents the reuptake of serotonin, and to a lesser extent, norepinephrine and dopamine, and facilitates release of these neurotransmitters [68, 139-141]. The selectivity of MDMA for specific monoaminergic neurotransmitters is species-dependent, and cannot solely be attributed to differences in binding affinity for specific reuptake transporters observed *in vitro*, as described below. In *in vitro* studies, MDMA was also found to compete with monoamines for sites on the vesicular monoamine transporter-2 (VMAT2), suggesting MDMA also promotes active release of monoamines from vesicular stores, in addition to inhibiting reuptake [142-144].

MDMA can inhibit monoamine oxidase A (MAO-A) *in vitro* at high concentrations, which preferentially degrades serotonin, and leads to accumulation of extracellular serotonin in the

synaptic cleft [145, 146]. Inhibition of MAO-A may have played a role in fatalities and medical emergencies seen after combining Ecstasy with MAO inhibitors in epidemiological settings [147, 148]. Spurred on by prior reports hypothesizing that apparent greater serotonergic toxicity of MDMA in primates, as compared to rodents, could be attributed to greater SERT affinity [149], researchers specifically examined affinity in cells transfected to express human monoamine transporters [141, 150]. These studies found that even though binding affinity of MDMA for the human norepinephrine transporter (NET) exceeded the affinity for SERT and dopamine transporters (DAT), serotonin was preferentially released over norepinephrine and dopamine [141], which may account for primarily serotonergic effects of MDMA. On the other hand, in rodents MDMA affinities for transporters are ordered as SERT>NET>DAT [151]. MDMA does not have as strong an affinity for the DAT as methamphetamine [21].

The ability of MDMA to stimulate release of pre-synaptic serotonin, norepinephrine, and dopamine in multiple brain regions and inhibit reuptake has been well documented [152]. *In vivo* microdialysis and voltammetry results show significant enhancement of serotonin, and to a lesser extent dopamine following MDMA administration, a response attenuated by various transporter inhibitors. MDMA-stimulated serotonin and dopamine release has been measured in the striatum, nucleus accumbens, PFC, and the hippocampus of freely moving rats [153-157], including after administering 0.32 to 3.2 mg/kg MDMA [157]. Female rats exhibited longer duration of nucleus accumbens dopamine, and longer duration of n. 5-HT after 1 and 3.2 mg/kg MDMA. In addition, enhancement of Ach release has been demonstrated in the PFC, striatum, and hippocampus by both a dopaminergic and serotonergic dependent mechanism [158, 159]. The subjective and physiological effects of MDMA are produced by the dynamic interaction of these transmitter systems on numerous brain networks that modulate learning and memory, emotion, reward, attention, sympathetic/parasympathetic activity, and neuroplasticity.

In addition to carrier-mediated monoamine release, MDMA has affinity *in vitro* for specific serotonin, norepinephrine, Ach, and histamine receptors, although the concentrations tested may not translate to standard human MDMA doses [24, 160-162]. An *in vitro* binding study comparing MDMA with several drugs that include cathinone derivatives suggests that contrary to an earlier report of low affinity for $5HT_{2A}$ serotonin receptors, MDMA may have significant effects at the receptor [25]. MDMA likely modulates $5HT_{1A}$ serotonin receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial $5HT_{1A}$ agonist in some brain areas [163]. Findings from other studies suggest that MDMA shares qualities with $5HT_{1A}$ agonists. Early studies in rats suggest that pharmacological activation of $5HT_{1A}$ receptors reduce anxiety and aggression [164, 165], and some drug discrimination studies suggest that the $5HT_{1A}$ agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) partially or fully substitutes for MDMA [166-168]. In addition to its primary effects, both enantiomers of MDMA enhance Ach release in the PFC [159, 169] and promote changes in GABAergic systems that correlate with sociability [170]. There is some evidence that $5HT_{2B}$ receptors are involved in stimulating increased locomotor activity in mice, reported in studies administering 20 mg/kg [171]. At least some direct or indirect effects of MDMA on serotonin receptors may alter GABA uptake in the ventral tegmental area of rats [172]. An *in vitro* study found that S-MDMA showed signs of competitive interaction with the alpha-4 beta-2 nicotinic receptor which are implicated in learning [173], while R-MDMA did not produce this effect [113].

Infusion of serotonin in the rat brain stimulates secretion of oxytocin into peripheral blood via activation of $5HT_{1A}$, $5HT_{2C}$, and $5HT_4$ receptor subtypes, as well as AVP secretion via activation of $5HT_{2C}$, $5HT_4$, and $5HT_7$ receptor subtypes [174]. MDMA was shown to increase oxytocin and AVP secretion in rats [175] through a $5HT_{1A}$ mechanism [176]. Administering a $5HT_{1A}$ antagonist attenuates the prosocial behavior of rats, measured by preference to lie adjacent to each other, possibly because it prevents elevation in oxytocin [176, 177]. MDMA also promotes

norepinephrine release through reuptake inhibition, which is an additional pathway that can contribute to oxytocin secretion and may control emotion regulation. Both oxytocin and AVP are implicated in the widespread regulation of behavioral aspects of mood and act on different target organs to modulate physiological functions in the periphery [178]. MDMA has been shown to have a diverse array of pharmacodynamic effects in animals, with findings of interest presented below by topic. Drug-discrimination and pre-pulse inhibition studies in rats lacking a SERT gene confirm the importance of the serotonin transporter in the interoceptive effects of 5 or 10 mg/kg MDMA, and its enhancement of pre-pulse inhibition (Pettie et al. 2018).

Findings from drug discrimination studies in rats suggest dose-dependent differences in the role of the serotonergic versus the dopaminergic system, with rats trained on 1.5 mg/kg MDMA recognizing SSRIs as similar while rats trained on 3.0 mg/kg recognized amphetamine as similar, and rats trained on both doses recognizing 5HT1A-related compounds as similar. Training with 1.5 mg/kg but not 3.0 mg/kg MDMA resulted in considering higher doses of a 5HT2A agonist a similar [179]. The same research team determined that dopamine antagonists interfered with the stimulus properties of amphetamine, but not MDMA [180].

4.2.2.1 Stable Effects on Gene Expression in Animals

Epigenetic modifications, including deoxyribonucleic acid (DNA) methylation, demethylation, and histone acetylation, are thought to be involved in dynamic regulation of memory reconsolidation in the adult nervous system and play a role in memory formation [181]. Early childhood adversity and trauma is associated with transcriptional silencing of the brain-derived neurotrophic factor (BDNF) gene through DNA methylation, which can either be a risk factor in development of PTSD or a result of having PTSD in adulthood [182]. In a 2015 report, MDMA showed DNA hypermethylation and hypomethylation activity in cardiac tissue by microarray analysis in mice [183], and this activity may extend to the CNS. Epigenetic effects on BDNF and other gene expression is one possible hypothesized mechanism by which MDMA in combination with training in animal studies modeling anxiety disorders, or psychotherapy in humans, exerts its therapeutic effects.

A number of research teams have studied the effects of MDMA on gene expression in rodents [184-189]. However, many of these reports used 10 to 20 mg/kg MDMA, a dose range that is 5 to 10.7 times greater than the 1.5 to 2 mg/kg doses employed in human trials, making it less likely that these changes can be generalized to humans given lower doses. However, even at these doses toxicity was not observed, and a self-administration study at clinically relevant doses reproduced findings of elevation of genes such as serum/glucocorticoid kinase 1 and 3 (*Sgk1*, *Sgk3*), which regulate glutamatergic signaling and are associated with neuroplasticity and learning, as well as processes involved in memory consolidation in serotonergic neurons [190]. These studies also report an increase in expression of genes that regulate the GABA transporter [184], which is expressed in GABAergic neurons indirectly regulated by glutamatergic afferent neurons. Serotonin-transporter knockout mice did not display some of these changes in gene transcription, suggesting that serotonin release is required for this activity [184]. In the acute period 24 to 48 hours after MDMA exposure, a study in rats found 33 to 70% upregulation of BDNF messenger ribonucleic acid (mRNA) transcripts in the frontal cortex, with a time-dependent decrease, up to 73%, of BDNF transcripts in the hippocampus [191]. The frontal cortex and hippocampus are both regions known to play a causal role in memory retrieval and reconsolidation in animals and humans [192], mediated in part through GABAergic signaling [193], suggesting that these transcriptional changes may be functionally related. An investigation of brains of Dark Agouti rats three weeks after 15 mg/kg MDMA, described in more detail in Section 4.4.10, that used get set analysis, reported different suites of downregulated and upregulated genes in frontal cortex and hippocampus, including genes related to long-term potentiation, presumed to be involved in

memory, neuronal plasticity and vitamin D receptors, without finding changes in serotonin transporter or tryptophan hydroxylase mRNA [185, 186].

Examining rat brains after repeated MDMA administration for 2 weeks detected a sharp drop in SERT expression [194], suggesting a compensatory downregulation in response to repeated high doses of MDMA. A study in rats found repeated administration of MDMA at 1 or 5 mg/kg weekly for 4 weeks increased transcripts for $5HT_{1B}$ receptors in various brain regions and $5HT_{2C}$ receptors in the cortex and hypothalamus, likely due to serotonin depletion and subsequent need to increase serotonin receptor availability [195]. Increased levels of gene transcripts regulating extracellular signaling in mice were also reported after MDMA [196]. Serotonin may play a more significant role than dopamine in transcription changes mediated by MDMA [195].
Findings in rats were confirmed in humans receiving a dose of 75 mg MDMA in the therapeutic dose range, which found increased expression of the SERT gene after MDMA when compared with placebo [197]. There was a trend for increased expression to be more pronounced in women and people with the l/l SERT genotype. Increased SERT gene expression after MDMA was associated with decreased arousal and increased fatigue.

Mouse brains examined 8 hours after 8 days of self-administration or non-contingent administration detected increased transcription of genes related to inflammation and immune modulation in both groups and transcription of genes related to neuroadaptation in mice self-administering MDMA [190]. Transcripts in these studies were assessed 8 to 10 hours after the last of repeated MDMA administrations and it is unclear whether these changes reflect residual acute effects of the MDMA, or changes related to repeated MDMA administration. In addition, changes in transcription do not always correlate with functional consequences in proteins levels. BDNF has been shown to have multiple functionally distinct splice variants which have tight temporal and spatial control in an activity-dependent, stimulus-specific manner [198]. However, MDMA produces a durable enhancement of fear extinction in mice, an effect mediated by an MDMA-associated increase in BDNF expression specifically in the context of fear extinction training, suggesting that gene expression changes after MDMA are functionally relevant [199].

4.2.2.2 Immunological Effects in Animals

MDMA acts as a mild immunosuppressant in rodents. MDMA administration at 5 mg/kg in rats is associated with impaired macrophage activity as evidenced by inhibition of Tumor Necrosis Factor-alpha (TNF-α) secretion for 12 hours post-drug [200]. In mice injected with 10 mg/kg MDMA for 5 days, increases in in epithelial tissue of cytokines interleukin 1-alpha (IL-1α), granulocyte-colony stimulating factor (G-CSF), and interleukin 3 (IL-3) were found, while decreased serum levels of many cytokines were reported [201]. MDMA decreased neutrophil oxidative bursts and phagocytosis and increased the number of circulating neutrophils while decreasing the number of lymphocytes. Incubating photoreceptor-generated cells with 0.5, 1 and 2 mcM MDMA activated macrophages and leading them to release proinflammatory cytokines [202]; it is unclear how this relates to immune system effects in humans. MDMA also increased hypothalamus-pituitary-adrenal (HPA) axis activity through a noradrenergic pathway in the hypothalamus [203]. MDMA also suppresses interferon-γ secretion and signaling in mice [204]. Interestingly, MDMA was shown to reduce inflammation and airway reactivity in a mouse model of allergic asthma, suggesting that MDMA could have beneficial immunomodulatory effects in cases of heightened inflammation [205]. This constellation of findings was in the 10 mg/kg dose range, which calls to question the applicability to moderate dosing regimens. However, a microarray study found that mice self-administering MDMA at moderate doses had transcriptional changes in many genes related to immune and inflammatory responses as well as neuroplasticity and learning [190], suggesting that immunosuppressant effects of MDMA at

clinically relevant doses could be beneficial in the treatment of psychoneuroimmunological disorders such as PTSD [206].

4.2.2.3 Thermoregulatory Effects in Animals

Rodents have generally been used to study the hyperthermic effects of MDMA. Rodents have a much smaller body mass and do not perspire but use their tail to regulate body temperature which has a large surface to volume ratio, and is perfused with many blood vessels for thermoregulation. Since thermoregulation is different in rodents and humans [207], findings may have limited applicability to humans. MDMA doses that are moderate to high elevate body temperature and disrupt thermoregulation in mice [137], and doses of MDMA in the 1 to 2 mg/kg range only cause a slight increase in body temperature [208]. Rats given doses of 10 mg/kg MDMA (s.c. and i.p.), but not 2 mg/kg, experienced increases in body temperature correlated with levels of the active metabolite MDA [86, 127]. A study of rats receiving subcutaneous injections of 1 and 3 mg/kg MDMA demonstrated minimal effect on brain hyperthermia using thermal couplers installed in the nucleus accumbens, and in another study, in the striatum [209], however ambient temperatures of 29°C and social interaction had a potentiating effect on body temperature and malignant hyperthermia at higher doses [210], described in Section 4.4 Toxicology in Animals and Epidemiological Settings. MDMA effects on body temperature are susceptible to changes in ambient temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperatures reducing it [211-213]. A study in rats found that age affects degree of body temperature elevation after 2 x 5 mg/kg MDMA, with 20-month old (aged) rats exhibiting significantly higher body temperature than young (40 days old) rats [214]. The aged rats in this study also exhibited more signs of brain and liver toxicity than younger rats. It is currently unknown whether MDMA-related increase in body temperature occurs in older humans. The MDMA-induced impairment in thermoregulation is caused, at least in part, by peripheral vasoconstriction in the tail, an effect mediated by brain neurotransmitter activity [215, 216].

High doses of MDMA also produce significant elevations in body temperature in primates [119, 217, 218]. At doses closer to those humans ingest [219], monkeys exhibit only slight to moderate elevation in body temperature [220, 221]. In contrast to findings in rodents, primates are not susceptible to changes in ambient temperature when given MDMA, exhibiting slight to moderate increases in body temperature regardless of the temperature of the environment [219-221], though at least one study found that the ambient temperature influenced the effects of 1.5 mg/kg i.v. MDMA on body temperature in monkeys, with lower body temperatures seen after MDMA administered in cool temperatures and higher body temperatures in another group given MDMA at warm temperatures [222]. Findings in rodents do not extrapolate well to primates in this area. Given that the thermoregulatory effects in rodents are highly dose-dependent, most physiological effects seen after low to moderate MDMA administration suggest that a controlled environment and moderate doses would be sufficient to mediate physiological complications associated with hyperthermia, including cardiovascular, osmoregulatory, neurological, and immunological effects.

4.2.2.4 Cardiovascular Effects in Animals

In vivo assessments of cardiovascular effects of MDMA in animals detected increased sympathomimetic activity, as seen in humans [137, 223]. An injection of 2 mg/kg MDMA elevated heart rate in rabbits [224]. Ten mg/kg MDMA produced a relatively larger increase in heart rate in rats than blood pressure, an effect possibly controlled by beta adrenergic receptors [223]. The researchers found that MDMA has both pressor and depressor effects, acting through adrenergic receptors [225-227]. Another study in rodents also suggests that norepinephrine may

play a role in cardiovascular effects [228], findings that have been more intensively investigated in humans [229-232]. When combined with ethanol, two 10 mg/kg doses of MDMA produced signs of cell stress in the right ventricle of mice [233]. Heart tissue from younger and older rats exhibited signs of vascular congestion after two or three doses of 5 mg/kg given two hours apart [214]. Given the affinity of MDMA for the NET, it is possible that the cardiovascular effects of MDMA could be partially attributed to norepinephrine signaling in the peripheral nervous system.

4.2.2.5 Osmoregulatory Effects in Animals

AVP is a key regulator of water balance in the body, and has antidiuretic actions when acting at its V2 receptor subtype in the kidneys [234, 235]. MDMA can influence water regulation by activation of the AVP system, as shown in several animal studies. A study of isolated *in vitro* rat hypothalamus initially reported AVP and oxytocin release after MDMA and its metabolite HMMA [33]. *In vivo* drug-discrimination studies in rats suggest that AVP receptors are involved in producing interoceptive effects of MDMA [178]. When 10 mg/kg i.p. MDMA was administered at 30°C ambient temperature to male Wistar rats, MDMA induced expression of Fos, a marker of neural activation, in the supraoptic nucleus, a brain region important for osmoregulation and a key mediator of oxytocin and AVP release [236]. This finding suggests that MDMA can have osmoregulatory effects in rats at high doses administered at warm ambient temperatures.

4.2.2.6 Neurobiological Effects in Animals

Most nonclinical research has focused MDMA toxicity in serotonergic neurons, while other studies have examined changes in neurohormones or effects on neuroplasticity. It appears that single doses of MDMA (2.5 mg/kg i.p. in monkeys, 7.5 mg/kg i.p. in rats), approximately four times a human equivalent dose, reduces brain serotonin production for 2 weeks or more [119] but does not increase validated markers of neurotoxicity associated with neurodegeneration [120]. Monkeys allowed to self-administer MDMA for an 18-month period had no reductions in brain dopamine, slight reductions in brain serotonin, and no chemical markers of neuronal injury [237]. One report detected a reduction in N-acetylaspartate to creatine ratio, which the authors considered a sign of neuronal injury, although no decreases in brain serotonin were detected after administration of two human-equivalent doses of MDMA to rhesus monkeys for 2 days [238].

A study examining the rat hippocampus reported indications of apoptosis after 5 or 10 mg/kg given daily for 1 week but not after 2.5 mg/kg [239]. A study in monkeys that counted rates of different types of neural progenitor cells combined with immunohistochemistry detected signs of reduced neurogenesis, but no signs of apoptosis, in the hippocampi after an intermittent regimen of ascending doses of MDMA from 0.5 to 2.5 mg/kg approximately every two weeks for up to ten months when compared with controls who did not receive MDMA [240]. This study used markers for Ki-67 cells, a type of activity dividing neural progenitor cells (NPCs), in the hippocampus, and cell death was measured via examining numbers of cells and caspase activation. The dose regimen is unusual in employing a long-term intermittent experimenter-administered dose regimen and using ascending doses.

Serotonin syndrome is defined as an excess of serotonin in the CNS causing a suite of specific signs and symptoms that can require intervention [241-243]. Doses of 10 mg/kg administered s.c. and i.p., but not 2 mg/kg, produced signs of serotonin syndrome in rats, but neither dose reduced total serotonin levels in the brain 2 weeks after drug administration. Serotonin syndrome severity correlates with MDMA plasma concentrations [86]. MDMA doses up to 2.5 mg/kg appear to alter regulation of serotonergic signaling in the rat brain without producing damage to serotonin axons,

based on transient reductions in brain serotonin and SERT levels, in the absence of indicators of neuronal injury or decreased expression of the SERT gene [96].

A series of studies examining neuritogenesis, a marker of neuroplasticity, found that MDMA and classic psychedelics stimulated neurite growth [244], with this BDNF-dependent effect blocked by $5HT_{2A}$ antagonists. MDMA was more efficacious than ketamine in promoting neurite growth. These findings may lie behind some of the therapeutic effects of MDMA, such as enhanced fear extinction learning, greater sensitization to prosocial effects and or re-learning or re-opening experiencing social reward, but behavioral effects were not specifically tested in this report.

MDMA suppressed midbrain serotonin neurons without having much effect on dopamine neurons in mice given 20 infusions of 0.125 to 5 mg/kg MDMA in a study comparing the effects heroin, nicotine, cocaine and MDMA in ventral tegmental area (VTA) [245]. The researchers were uncertain as to the cause of this effect but established that a $5HT_{1A}$ antagonist reduced the suppression, suggesting the involvement of serotonin autoreceptors. While individual doses of MDMA are similar to human-equivalent doses, cumulative doses of infusions ranged from 2.5 mg to 100 mg. It is notable that the researchers found heroin to increase dopaminergic cell activity while finding that cocaine, like MDMA, suppressed serotonergic activity as well as dopaminergic activity. Given these mixed findings, it is unclear how this relates to models of reward value or abuse liability.

In rats, large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin [246-248], with elevations lasting up to 4 hours after dosing, and with hormone levels attenuated by a $5HT_{2A}$ serotonin receptor antagonist. Given the dosage used was five to 10.7 times larger than an active dose in humans, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. Administering 1 to 3 mg/kg doses found that R(-)-MDMA, but not S(+)-MDMA, significantly increased prolactin levels in rhesus monkey plasma, suggesting that at least the R(-) enantiomer of MDMA can influence endocrine signaling at doses relevant for studies in humans [23]. Fluoxetine attenuated prolactin release after administration of racemic MDMA, and fluoxetine and a $5HT_{2A}$ antagonist attenuated prolactin release after R(-)-MDMA, indicating that prolactin release is associated with serotonin release and indirect action on $5HT_{2A}$ receptors by R(-) -MDMA [110].

Serotonergic deficits are associated with disruption of sleep patterns and architecture. In drug-naïve rats, a single dose of 15 mg/kg MDMA i.p. contributed to marked increases in motor activity, deep slow wave sleep, and wakefulness for 5 to 6 hours. Circadian patterns of motor activity and sleep/vigilance parameters were altered for up to 5 days post-treatment, after which most parameters returned to normal. In a single exposure to MDMA 3 weeks prior to the same procedure, rats experienced the same acute effects, but with shorter duration, suggesting that MDMA has the ability to influence sleep architecture and patterns acutely after this dose in drug-naïve rats, but these effects are mediated by experience with MDMA and do not persist beyond 1 week [249]. A study comparing saline, racemic MDMA and R-MDMA (0.3 to 1.7 mg/kg i.v.) given in the morning versus afternoon reported no differences in sleep onset or wake time after morning administration [250]. Racemic and R-MDMA reduced wake time after sleeping, and when administered in the afternoon, racemic MDMA delayed sleep latency. As of 2019, the only comparable human trial administered MDMA in the evening, but also crossed administration with sleep deprivation and used a supplemental dose regimen [251]. However, the results in monkeys indicate that time of administration can influence sleep quality.

4.2.2.7 Neuropsychological Effects in Animals

In rodents, doses of MDMA equivalent to human doses produce few behavioral effects. However, several dose-dependent differences on behavioral tests in rats have been reported, including increased locomotor activity and anxiety-related behaviors thought to be associated with serotonin syndrome [177, 252], and decreased social anxiety at 5 mg/kg i.p. [177]. Rats given 7.5 mg/kg MDMA, equivalent to four times the dose tested in humans, exhibited increased anxiety in the elevated plus maze [253], while rats given 15 mg/kg MDMA, equivalent to eight times the dose tested in humans, exhibited reduced anxiety on the maze. A study in mice reported that doses from 0.5 to 20 mg/kg produced anxiogenic responses on the plus maze [254]. A study of the sub-acute effects of four different doses of MDMA given daily for 1 week, found reduced anxiety with 1.25 and 2.5 mg/kg and increased anxiety with 5 and 10 mg/kg [239]. Lower doses used in these studies are comparable to dose used in human research and nonmedical settings. However, sample sizes used in the study were small. Rats given higher doses also reduced aggressive behavior as well as social investigation. Mice placed in the forced-swim test, an animal model of antidepressant action, exhibited less immobility after acute doses of 2.5, 5 and 10 mg/kg MDMA, considered an indicator of antidepressant activity [254]. However, as noted above, MDMA can increase locomotor activity.

MDMA produces some repetitive behavior in rodents, but not to the same degree as psychostimulants. Rats on MDMA walk around a cage perimeter, interpreted as an indicator of thigmotaxis, which is a sign of anxiety [137]. However, it is notable that a 2007 publication failed to find thigmotaxis in rats given 5 mg/kg MDMA [255]. Increased locomotion in rodents after MDMA may regulated in part by $5HT_{2C}$ and $5HT_{2B}$ receptors, possibly through indirectly regulating dopamine and serotonin release [171, 256], and at least one study reported that blocking alpha1 adrenergic receptors reduced locomotor activity after 5 mg/kg MDMA [255]. In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA [221].

Some researchers have proposed that behavioral tests of anxiety may instead be measuring risk-taking behavior, or impulsivity [257]. It is also notable that the majority of rat studies with deleterious behavioral findings were conducted specifically in inbred male Wistar rats, suggesting that individual and gender-based differences could influence these findings [258, 259]. Preclinical data in animals suggests that the profile of neurotransmitter release observed after MDMA administration may increase the risk of mania in some individuals [260], although mania has not been a reported as a side effect of MDMA or Ecstasy in humans. Conflicting findings on anxiogenic and anxiolytic dose-dependent effects of MDMA are likely to have limited applicability to humans, with transient anxiety being a possible side effect.

Morley and colleagues observed rat behavior after receiving 5 mg/kg MDMA, noting that this dose correlated with prosocial behavior, such as lying next to each other [177]. Subsequent studies suggest that MDMA increases prosocial behavior in rats by elevating oxytocin in the paraventricular nucleus through $5HT_{1A}$ receptor agonism, with the oxytocin increase arising from the indirect effects of MDMA on $5HT_{1A}$ receptors via serotonin release [176, 261, 262]. There have been no human pharmacological challenge studies combining MDMA with $5HT_{1A}$ agonists, while $5HT_{1A}$ antagonists have negligible effects on subjective or physiological effects of MDMA in humans [100, 263-265]. As a result, it is unclear whether the rat behavior is analogous to human reports of increased feelings of empathy or interpersonal closeness while under the influence of MDMA [2, 13, 266, 267]. Pitts and colleagues reported observing greater prosocial effects of MDMA when compared with the psychostimulant methamphetamine in squirrel monkeys [268], confirming rodent findings in primates. The effects were seen with racemic MDMA and with each enantiomer, and they were dampened by administration of a $5HT_{2A}$

receptor antagonist. MDMA appears to have prosocial effects on animals less closely related to humans, including octopuses and zebrafish [269, 270]. The study in octopuses examined the octopus serotonin transporter gene, determining that the receptor that binds MDMA is conserved across species.

The social effects of MDMA may also include setting-dependent acute social sensitization and extension of a critical period of increased sociality in mice. In mice, MDMA may sensitize mice to social interactions with unfamiliar mice via setting-dependent sensitization [271]. After an initial dose of MDMA (7.8 mg/kg) in the company of an unfamiliar mouse, a subsequent dose produced greater social interaction. The same effect did not occur when preceded by a social setting or MDMA in a nonsocial setting, and the effect can be antagonized by blocking $5HT_{2A}$ receptors. Adult mice exhibited a greater desire to be with another mouse two days after receiving MDMA (10 mg/kg) [272], re-opening a critical period for learning social reward that generally declines during adulthood. This effect appears tied to upregulation of oxytocin receptors in the nucleus accumbens. These effects may support posited therapeutic effects in humans, such as increased rapport with therapists and greater ability to have fulfilling interpersonal relationships.

MDMA given before training persistently enhanced fear extinction learning in mice through a BDNF-dependent mechanism [199], which could be a possible mechanism of action for MDMA in combination with psychotherapy as a treatment for anxiety disorders. The dose of 5.6 mg/kg was approximately two times a human equivalent dose based on plasma values, but the findings are the first biological evidence of a lasting effect of MDMA on disruption of anxiety-related behavior in mice. MDMA, (1 mg/kg, 2,5 and 5 mg/kg, not 1 or 10 mg/kg) given alone or with nicotine, enhanced consolidation of recall for a passive-avoidance task, a different type of fear memory [254, 273]. A fear extinction study in rats failed to replicate an enhancement of fear extinction, finding instead that 3 and 5 mg/kg MDMA administered prior to training impaired fear extinction learning, while MDMA administered during reconsolidation produced persistent reduction in fear [274].

4.3 Physiological Effects in Epidemiological Settings

The vast majority of non-clinical epidemiological studies are retrospective comparisons of people who have previously self-administered Ecstasy, a study design that is unable to eliminate the possibility that one or more predisposing factors may lead to repeated Ecstasy use and the variables compared [5, 97, 275]. Samples are often selected on the basis of moderate to heavy self-reported Ecstasy use, with very few studies conducted in samples reporting the levels of moderate exposure seen in clinical trials. Many investigations have compared people reporting use of Ecstasy with non-Ecstasy using controls, mostly as a means of detecting long-term effects of Ecstasy use. Many of the studies do not appropriately match samples for substance use behavior, there is often concurrent use of other illicit substances and the Ecstasy used is of unknown purity, dosage, and composition.

The acute effects of MDMA have an initial onset of approximately 30 minutes after oral intake and are characterized by anxiety, tachycardia, and elevated blood pressures [276]. Typical effects include diaphoresis, bruxism, jaw clenching, paresthesias, dry mouth, increased psychomotor activity, and blurred vision. Within an hour, these sympathomimetic effects are replaced by feelings of relaxation, euphoria, increased empathy, and communication. Taking a smaller supplemental dose may prolong these effects and this is being tested in the context of clinical trials. However, when too much additional MDMA is consumed in an uncontrolled setting, individuals report unpleasant symptoms of autonomic hyperarousal associated with feelings of restlessness, paranoia, and anxiety. With increased dosage sympathomimetic effects predominate,

placing the patient at risk for cardiovascular instability, arrhythmias, and hyperthermia (see Section 4.4 Toxicology in Animals and Epidemiological Settings).

Retrospective surveys of Ecstasy use offer similar accounts of subjective effects to those reported in controlled studies of MDMA. Study respondents report experiencing stimulant-like effects, such as greater energy or talkativeness, and hallucinogen-like effects, including perceptual changes, visual distortions, or poor concentration, as well as feelings of closeness, compassion, or empathy toward the self or others [2, 266, 267, 277-279]. The disparity in detection of entactogenic effects in retrospective versus controlled studies is largely due to failure to measure these effects, but might also relate to aspects of setting in controlled studies that do not permit enough unstructured interpersonal contact to produce or facilitate feelings of interpersonal closeness. Starting in the 2010s, more researchers are seeking to assess the prosocial effects of MDMA [37, 40, 41, 280].

The findings discussed in this section are of effects in low to moderate users of Ecstasy. Serious and life-threatening events and effects in heavy users are discussed in Section 4.4 Toxicology in Animals and in Epidemiological Settings. Because of these many confounds and issues, findings discussed from retrospective comparisons and case reports of Ecstasy using samples and controls are considered cautiously with respect to their degree of relevance for safety in clinical trials.

4.3.1 Immunological Effects

As supported by mild immunosuppressant effects found in rodents, a longitudinal study of regular Ecstasy and cannabis users found a sustained reduction in IL-2, increased levels of Transforming Growth Factor-Beta (TGF-ß), and reduced CD4 cells, and regular Ecstasy and cannabis users reported experiencing a greater number of mild infections than occasional Ecstasy and cannabis users on a structured questionnaire [281]. Immunological effects of MDMA in humans are likely to involve serotonergic pathways and are discussed in more detail in Section 5.3.2 Immunological Effects.

4.3.2 Thermoregulatory Effects

Thermoregulatory effects of Ecstasy taken in epidemiological settings are highly dependent on dose [282] and permissive factors, including high ambient temperature [283, 284], crowded conditions involving overwhelming social interaction, physical exertion, reduced fluid intake [283], and thyroid dysregulation [285, 286]. In the absence of these permissive factors from use in epidemiological settings, hyperthermia is rarely reported.

For a detailed discussion on thermoregulatory effects when Ecstasy is combined with permissive factors, see Section 4.4.6 Hyperthermia.

4.3.3 Cardiovascular Effects

Studies in Ecstasy users indicate that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities [287]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Previous to this, echocardiographic readings in eight Ecstasy users also failed to find any cardiac abnormalities [52]. Valvular heart disease (VHD) only occurred after extremely heavy Ecstasy use; therefore, it is unlikely to be a risk within the research or therapeutic context where participants are screened for relevant pre-existing conditions. For more information on toxicological effects, see Section 4.4.7 Cardiovascular Toxicity.

4.3.4 Osmoregulatory Effects

Ecstasy use has been associated in the literature with acute symptomatic hyponatremia with the syndrome of inappropriate antidiuretic-hormone secretion (SIADH) involving raised antidiuretic-hormone, also known as AVP [288]. SIADH refers to disorders related to water and sodium balance characterized by the impairment of urinary dilution and hypotonic hyponatremia in the absence of renal disease or other identifiable non-osmotic stimuli known to activate the release of AVP [289]. MDMA is known to cause central release of both oxytocin and vasopressin through indirect effects of serotonergic signaling as previously described, and this activity indicates that it is not accurate to attribute the osmoregulatory effects of Ecstasy to SIADH, but rather this should be characterized as a pharmacological effect on AVP secretion.

AVP plays a key role in osmoregulation, and is released upon a change in plasma osmolality [290]. AVP is also involved in the response and adaptation to stress, through its effects on the HPA axis [290]. The rise in AVP does not seem to be part of a generalized stress response, but results from a pharmacological effect compounded by excessive fluid ingestion [291]. In Ecstasy users with confirmed urinary MDMA, a significant association was found between plasma osmolality, plasma sodium, and CYP2D6 extensive metabolizer/ intermediate metabolizer genotypes and COMT low-activity genotypes [292]. Effects of Ecstasy, combined with increased consumption of water and permissive factors, such as strenuous exercise in warm ambient temperatures, can be further exacerbated in the context of poor metabolism. Gauging appropriate water intake may be difficult for users to estimate because MDMA reduces perception of thirst and impairs judgment [293]. For more information on the risk of hyponatremia, see Section 4.4.8 Hyponatremia.

4.3.5 Neurobiological Effects

Spurred on by animal studies that found repeated or high doses of MDMA damaged the axons of serotonin neurons, researchers began studying the effects of repeated non-medical or recreational use of Ecstasy in humans [91-93, 294]. Early investigations had several methodological flaws, including retrospective design and poor matching of Ecstasy users with appropriate controls [97, 295]. Later studies sought to remedy some of these problems by using carefully matched polydrug user or cannabis user controls, or by relying on a sample with relatively low exposure to psychoactive substances, including alcohol [296-299]. Researchers comparing the average reported Ecstasy/MDMA use of samples in imaging studies with average use in a large, global internet survey found participants in imaging studies were in the top 5 to 10% in terms of size of usual dose and amount taken per occurrence [300]. Imaging studies may not represent effects in people reporting average use, or in people enrolled in clinical trials. Some of these investigators also conducted longitudinal studies, comparing Ecstasy users, sometimes alongside controls, at two separate time points [301-303].

Researchers using slightly different methods have reported differing results. These include finding no differences between Ecstasy user and polydrug user controls in SERT binding sites [304], modest reductions in estimated SERT sites in Ecstasy users versus non-drug using or cannabis-using controls [305], and an association between decreased SERT sites and lifetime Ecstasy use [306]. This study also reported finding slightly fewer $5HT_{2A}$ receptor binding sites in both "Ecstasy preferring" and "hallucinogen preferring" groups. Studies in low to moderate Ecstasy users did not report an increase in this marker [307], and only one of three studies in heavy users detected a change in $5HT_{2A}$ receptor density. [308-310]. A systematic meta-analysis of imaging studies collected up through August 2018 detected reduced SERT binding in eight of 13 regions examined, including parietal, temporal and occipital lobes, anterior and posterior cingulate, thalamus, and hippocampus with reduced SERT sites associated with duration of

abstinence [311]. The lack of association between reduced SERT binding and lifetime episodes of use might be related many imaging studies sampling from people already reporting high lifetime Ecstasy use, and removal of one study from the analysis eliminated the association with time since last use. A prospective study in moderate Ecstasy users also failed to find any chemical markers of neuronal injury, and only found decreased cerebral blood volume in the dorsolateral frontal cortex [307, 312]. The same meta-analysis, described above, also failed to find any association between Ecstasy use and chemical markers of neuronal injury or CBF changes in basal ganglia [311]. A re-examination of brain imaging using the less specific SERT marker Beta-CIT indicate an inverse relationship between age of first use of Ecstasy and mid-number of midbrain serotonin sites without detecting any relationship between age of first use and frontal SERT sites [313]. A retrospective imaging study using a radioligand that maps serotonin synthesis found lower ligand presence ("trapping") in prefrontal, orbitofrontal and parietal areas and higher presence in brainstem, frontal and temporal areas in Ecstasy users versus polydrug user controls, with a greater difference seen in men [314]. The researchers reported relationships between differences in trapping and cumulative use, duration and temporal proximity of use. The samples were not well-matched for drug use.

Studies comparing brain activity in Ecstasy users and non-Ecstasy using controls reported some but not many differences in brain activity. These included greater brain activation in the occipital cortex, with concomitant methamphetamine use contributing to increased activation to a visual stimulus [315]. The same group of researchers detected less within-region coherence in the thalamus in Ecstasy users who averaged 29 episodes of use when compared with non-Ecstasy-using controls [316]. In a retrospective study, Ecstasy users exhibited lower brain activity in bilateral dorsolateral prefrontal cortex compared with controls reporting no illicit drug use, with neither group exhibiting impaired task performance [317]. Ecstasy users exhibited a single difference in brain activity compared to polydrug using controls. A prospective study comparing brain activity before and after use of Ecstasy failed to detect differences in working memory, attention or brain activity [318], suggesting a relationship between repeated, regular use of Ecstasy and other drugs and changes in brain activation. Investigations of the interaction between genotype and regular Ecstasy use have supported differential effects upon reward-based attention or visual or verbal memory [319-321], with some findings supporting differences due to genotype and some failing to do so. A systematic examination of imaging studies comparing ecstasy users reporting consumption of 100 or fewer tablets with controls reported finding no evidence for an association between moderate Ecstasy and signs of structural or functional changes in the brain [87]. Given the small samples and uneven numbers with different genotypes, any conclusions await further support.

Sleep disturbances are thought to be associated with deficiencies in serotonergic signaling [322]. Examining sleep architecture in Ecstasy users, investigators found less total sleep time and less stage 3 and 4 sleep on the adaptation night, but no overall differences in sleep architecture [323]. Another study comparing heavy Ecstasy users with non-drug using controls found no differences in baseline sleep using electroencephalography (EEG) [324]. Early studies in mostly heavy Ecstasy users reported significant decreases in total sleep as well as stage 2 sleep [325], while studies conducted in the 2000s found Ecstasy users were able to fall asleep more easily upon depletion of catecholamine neurotransmitters suggesting an underlying difference in serotonergic control of sleep architecture [326, 327]. Findings of sleep disruption in Ecstasy users are not likely to be applicable to the exposures seen in research or therapeutic settings.

A study of breathing during sleep in 71 Ecstasy users and 62 polydrug users did not find overall differences in disrupted breathing, assessed via nasal cannula, but found that all moderate and severe breathing disruptions occurred in the Ecstasy using sample [328]. McCann and colleagues reported a relationship between cumulative (lifetime) Ecstasy exposures and instances of

disrupted breathing during non-REM sleep and suggested Ecstasy users could be vulnerable to potentially fatal sleep apnea. In contrast, other researchers failed to find greater night-time awakenings indicative of sleep apnea in Ecstasy users [323, 324], and the high rate of disrupted breathing McCann and colleagues detected even in the controls suggest that this measure may not provide clinically significant assessments. Taken together, it appears that MDMA acutely produces lighter sleep with fewer REM periods.

4.3.6 Neuropsychological Effects

Previous reports have found an association between Ecstasy use and symptoms of depression or anxiety [329, 330]. A meta-analysis of self-reported depressive symptoms detected an association between Ecstasy use and scores on the Beck Depression Inventory (BDI), a popular self-report measure of depression symptoms [331]. However, the association was strongest in studies with small samples, and drug use variables were often incompletely reported and not verified through any methods save self-report in the studies analyzed. Many studies found that increases in self-reported anxiety or depression were more strongly related to polydrug use rather than to use of any one substance [332-335]. Two studies found an equal or stronger association between regular use of cannabis, and not Ecstasy, with anxiety, depression or other psychological problems [336, 337]. An assessment of men reporting substance use in a large cohort found that the highest degree of mental health problems in respondents reporting Ecstasy use in the last 12 months, followed by those reporting stimulant use [338]; stressful life events and perceived stress also differed across groups. Anxiety regarding loss of control under the influence of Ecstasy could develop to a degree where it could lead to panic attacks. Case reports have been published describing panic attacks in individuals under the acute influence of Ecstasy [339]. Enduring panic attacks have been reported in individuals after repeated Ecstasy use [340, 341] and in one case, even after a single dose [342].

When compared with polydrug using controls, people who use Ecstasy report being more empathetic and exhibit greater cognitive empathy when viewing photographs of expressive emotions [343], and did not differ in degree of reaction to social exclusion. These findings may be affected by the same problems as other retrospective studies, such as the presence of another factor or factors influencing empathy and drug use patterns.

Neuroendocrine response to oral citalopram did not differ between Ecstasy users, cannabis users and controls [344]. People reporting regular drug use and Ecstasy use had higher levels of salivary cortisol in the evening, and higher salivary cortisol on the day of a multitasking activity [345], and higher salivary cortisol on waking that was unrelated to prefrontal SERT binding or self-reported depression symptoms [346]. A 4-year longitudinal study reported that factors other than Ecstasy use, including female gender and presence of financial and relationship difficulties, were more closely related to self-reported symptoms of depression [347]. Comparison of self-reported psychological symptoms in samples of people grouped by self-reported drug use found current Ecstasy users had lower global symptom severity scores than polydrug users [348]. In conclusion, it appears that the relationship between Ecstasy use on self-reported mood or psychiatric problems is not strong, with equal or stronger involvement of other factors.

In a prospective study comparing cognitive function in people before and up to 18 months after reported initiation of Ecstasy use, Schilt and colleagues found an association between Ecstasy use and performance on measures of verbal memory, but not attention or working memory [349]. All scores were within normal range; people who did not use Ecstasy showed greater improvement in performance at the second time of assessment than people reporting some use. A second prospective study examined working memory in people reporting Ecstasy use similar to participants in Schilt's study with controls, and failed to find any significant differences in

working memory and selective attention [318]. An analysis of findings from largely retrospective studies of Ecstasy users reported a small deficit in verbal or working memory [61]. Retrospective studies of polydrug users who use Ecstasy and controls reported impaired global motion processing without changes to local processing [350].

Not all studies report that Ecstasy users fare worse on measures of cognitive function than controls, and methodological critiques and at least one commentary and review discuss the contribution of research and publication bias in driving findings [351]. Several reports detected little or no significant differences between Ecstasy users and polydrug user controls in performance on tasks of cognitive function [275, 317, 318, 352-356], though other studies continue to find consistent differences, particularly in verbal memory [327, 357-360]. Regular use of many substances, including alcohol, may affect cognitive function, with Ecstasy being only one of those substances [361]. Several reports have found relationships between cognitive function and use of other drugs as well as or instead of Ecstasy [320, 352, 354, 357, 362, 363].

The only study attempting to address effects of Ecstasy use on cognitive function in middle aged versus younger users did not find a greater degree of impairment. Schilt and colleagues reported impaired verbal memory in people who began using Ecstasy in their 30s compared with age-matched drug-naïve and polydrug using controls reporting some lifetime Ecstasy use, but did not find a greater effect size for Ecstasy use in this sample than in samples of younger Ecstasy users, leading them to conclude that Ecstasy use does not have a greater impact on cognitive function in older users [364].

The relationship between Ecstasy use and impulsivity has also been extensively examined, with some researchers reporting greater impulsivity in Ecstasy users and others failing to find any differences [92, 365]. Studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions [356, 366, 367]. Two studies using the same measure of behavioral impulsivity in samples of heavy Ecstasy users obtained different findings [356, 366]. It is notable that Quednow and colleagues compared Ecstasy users with abstinent cannabis users and drug-naïve controls while Roiser and colleagues compared Ecstasy users with former Ecstasy users, polydrug users and drug-naïve controls, raising the possibility that results might have differed in part due to control group selection. It is possible that people who self-administer Ecstasy may already possess above-average levels of sensation-seeking and impulsiveness. To date, all such studies have used retrospective study designs and cannot rule out this possibility, and some studies suggest that polydrug use may be equally or more strongly related to impulsivity in Ecstasy users [368-370]. Authors of a systematic review of decision-making that addressed many of these studies concluded that the current research does not permit drawing conclusions concerning effects of long-term ecstasy use on decision-making [371]. Adolescents "at risk" for stimulant use, including MDMA, reported greater rates of gambling than at-risk adolescents not reporting stimulant use, with gambling considered a possible marker of impulsivity [372]. The relationship between drug use, including Ecstasy use, and impulsivity, is complex, including likely contributions of impulsivity and risk-assessment decisions on the decision to initiate and continue ecstasy use that make it difficult to assess causality.

4.4 Toxicology in Animals and Epidemiological Settings

In the sections below, nonclinical toxicological findings are presented for animals and epidemiological studies or case reports of morbidity and mortality in Ecstasy users. Data from epidemiological studies are provided, subject to the limitations in interpretation that result from unknown purity, dose, and quantity of MDMA existing in Ecstasy use in naturalistic settings.

4.4.1 Single Dose Studies in Animals

Single doses between 5 and 60 mg/kg have been administered in rodents. Since rodents are similar to primates in mg/kg dosing, the doses of 5 mg/kg and above, administered by any route of administration in rodents, are inappropriately high for comparison to human studies utilizing doses less than or equal to 125 mg, so findings are only useful as models of toxicology or abusive use in humans. A study of the long-term effects of a single dose of 5.7 mg/kg MDMA on estimated SERT sites in the brains of squirrel monkeys reported reduced sites in some frontal, temporal and parietal areas [373]. The plasma C_{max} of 725 µg/L in squirrel monkeys was three times greater than what is observed in humans after a single dose of 100 mg MDMA (C_{max} of 202.92 to 222.5 µg/L) [126, 374, 375], even after administration of a supplemental dose twice that of the initial dose 2 hours later, which increased C_{max} to 311.16 µg/L [375]. A handful of studies in rats have examined the effects of single toxic doses in comparison to low doses and determined that single doses have transient effects on serotonin depletion [86, 127, 132], likely due to reversible inhibition of tryptophan hydroxylase [17, 18, 20], which prevents additional serotonin from being produced and released.

Researchers administered 15 mg/kg MDMA to Dark Agouti rats in studies intending to examine brain region specific changes in gene expression subsequent to a single, presumably neurotoxic dose of MDMA [185, 186], examining brains three weeks after drug administration. Petschner and colleagues reported downregulation of calmodulin and glutamate receptor related genes in the frontal cortex (CAMk2g, CAMk1g, Grin2B, a heat shock protein subunit (Hspca) and glutamate transporter (Slc1a3). In the hippocampus, they reported changes in expression of several glutamate receptor genes (Gria1, Grin2a), calmodulin related genes (Camk2g, Camk2b, Kalrn, EphA4), the GABA-A receptor (Gabre), several calcium transport genes (Atp2b3, Atp2b1), and the cannabinoid receptor CB1. Most showed downregulated expression; Gabre and the calmodulin gene Camk2n2 were upregulated. They summarized these findings as indicative of reductions or changes in memory and cognition.

In a separate report, Petschner and colleagues report detecting changes in vitamin D receptor genes, considering them a sign of response to oxidative stress [185]. Focusing on the hippocampus, the researchers reported upregulation of one gene and downregulation of 13 genes, including Pax4, Pitx2, FoxJ2, FoxO1, Oct1, Sp3, AP3, FoxO4, and vitamin D receptor genes. The intended activity or purpose of five of these genes, was unknown at the date of publication (2018), including the upregulated gene ACTWSNACTNY_UNKNOWN. Gene set analysis (GSEA) reported that genes expressed three weeks after 15 m/kg were connected to vitamin D. . The researchers were unable to detect signs of reduction in SERT or tryptophan hydroxylase (no reduction in mRNA). Since brains were examined weeks after drug clearance, the authors hypothesize that changes in genetic expression represent or explain changes in memory and cognitive function in people reporting extensive Ecstasy use, and recovery from oxidative stress. Since the techniques employed are relatively new, introduced in the mid-2010s, and no comparisons exist for changes after lower doses of MDMA, interpreting numerous changes should be considered tentative.

An investigation combining social defeat with a single dose of 10 mg/kg in mice detected additive effects of social defeat and MDMA on measures of memory and anxiety and depression made one to ten days after drug administration. Social defeat and MDMA both affected passive avoidance and object recognition memory, and the combination of the two produced greater memory impairment. Social defeat and MDMA also increased immobility in the tail suspension test, and increased motion and increased tendency to remain in the center of the open field, [376]. Administering an additional 5 mg/kg MDMA in the open field resulted in slower speed in mice that underwent social defeat and received MDMA. Social defeat immediately followed by

MDMA increased lowered body temperature and reduced blood cortisol, assessed in a sub-sample of mice, and the authors refer to this as evidence for stress enhancing impaired cognition and depression-like behavior after MDMA. However, they did not employ a test of direct effects of corticosterone, and it is possible that social defeat and MDMA produce independent effects.

4.4.2 Repeated Dose Studies in Animals

The majority of toxicological studies employed multiple dosing regimens to account for the shorter drug half-life in animals compared to humans, with doses ranging from 5 mg/kg to 20 mg/kg, via s.c., i.p., oral, or gavage administration. Frequently, doses are administered at regular intervals of two to four times per day. Other regimens employ these doses once daily for 5 or 7 days. Nearly all preclinical toxicology data is derived from repeated dose studies. Preclinical research selected doses through use of simple dose conversions or allometric scaling, a method of modeling human equivalent doses in other species [377]. Comparison of pharmacokinetic data ($C_{max,}$ AUC, T_{max}) for plasma MDMA concentrations between humans and rodents, considering the impact of route of administration, it is difficult to translate the relevance of high dose multi-day dosing findings in preclinical toxicity studies to intermittent dosing regimens in humans.

In order to establish the DMF and IND for MDMA, MAPS sponsored randomized 28-day repeated dose general toxicity studies in both genders of Sprague-Dawley rats (53 male, 52 female) (MDMA 0, 10, 50, 100 mg/kg oral gavage) and the dog (12 male, 12 female) (MDMA 0, 3, 9, 15 mg/kg oral dosing with gelatin capsules) [378]. The initial highest dose was set at 18 mg/kg but after the death of one female dog, the highest dose was subsequently reduced to 15 mg/kg. Dosing was once daily for 28 days. This research was performed within the USA, which is a member of the Mutual Acceptance of Data (MAD) program, and studies were conducted in compliance with GLP in the USA based on standards in 1986 to the satisfaction of FDA. Both sexes of dogs administered 9 and 15 mg/kg of MDMA and rats receiving 50 and 100 mg/kg gained less weight than controls and the 3 mg/kg group, with significant differences in food consumption observed as early as the first week which were no longer significantly different by the third week for the rats and the fourth week for the dogs. Gross observations at necropsy in the dog possibly related to MDMA included reduced testicular size for one of three dogs receiving 9 mg/kg and one of three dogs receiving 15 mg/kg and prostatic enlargement in two dogs receiving 15 mg/kg. No gross lesions were seen in the rats at necropsy. Blood chemistry and urinalysis values were unremarkable in the dog. Clinical pathology findings showing a trend to decrease with dose in the rat were urinary pH, blood urea nitrogen, glucose, creatinine (females), lactate dehydrogenase (females), and chloride, in contrast total white blood cell count (WBC) and phosphorus showed a trend to increase with dose. No MDMA-related lesions were seen in the brains of either species. Histopathological examinations showed mild, diffuse atrophy in the two dogs with reduced testicular size. Mild, focal atrophy was furthermore observed in the testes of one additional dog from the 15 mg/kg group. The two dogs with grossly enlarged prostates showed hyperplasia of the prostate. Brain lesions attributable to MDMA were observed in five of ten male rats administered 100 mg/kg (no lesions were observed in females). These lesions presented as vacuolated lesions apparent in the fiber tracts of the brainstem adjacent to the trigeminal nuclei. Possibly MDMA-related lesions were observed in the CNS of the dogs as well. In the cerebrum, these lesions included floccular changes of white matter, focal neural malacia and focal cellular infiltrates. Neural chromatolysis was observed in the brainstem. However, the authors noted that it is difficult to extrapolate the findings due to the low sample size (three dogs per gender per group).

A study administering Sprague-Dawley rats 40 mg/kg or 80 mg/kg of MDMA twice a day for four days showed no morphological brain changes. Neurochemical brain changes related to MDMA administration included a 50% decrease in serotonin (5-HT) and 5-Hydroyindoleacetic

acid (5-HIAA) at both dosing levels. This decrease was apparent both two and four weeks after treatment. A temporary 34% decrease in homovanillic acid (HVA) was observed in the 80 mg/kg group at two weeks after treatment. Four weeks after treatment the HVA levels had returned to normal. These findings indicate that several, high dose administrations of MDMA produce long term reductions (4 weeks) in 5-HT and 5-HIAA in the rat while having no apparent effect on the dopaminergic system. [379]

In a sponsor-supported study of Sprague-Dawley rats, oral toxicity was assessed in a 13-day increasing dose regimen [380]. The initial dose started at 25 mg/kg and was increased by 25 mg/kg on a daily basis until 300 mg/kg was reached. Adverse reactions were observed in all doses above 25 mg/kg and included hyperexcitability, uncontrolled urination, piloerection and bulging eyes. Tremors, muscle spasms, impaired movement, convulsions and death were observed in the highest of dose levels (not listed in original report). Deaths occurred at doses in the range of 150 and 300 mg/kg. Blood chemistry analyses suggested possible liver and kidney damage in animals receiving higher doses, however, gross pathology and microscopy found no treatment-related damage to the liver. The only renal change observed microscopically was mild to minimal hydronephrosis, which the researchers attributed to treatment-related polyuria (abnormally large urine production). Minimal tubular atrophy was seen in the testes of 3 of the 20 treated male rats, suggesting a possible relationship between high dose, repeated MDMA treatment and minimal testicular atrophy in the male rat. Gross pathology revealed reddened lungs and enlarged urinary bladders (most likely polyuria-related) in some animals and were deemed potentially treatment-related. Histopathological observations of brain tissue revealed no signs of brain damage in any of the treated rats.

Findings from an examination of ovarian tissue in vitro and in vivo (5 mg/kg daily x 3) reported effects seen in vitro, such as resuming meiosis, but in vivo exposure did not produce changes in gene activity in ovarian cells [381]. The authors acknowledge differences in metabolism between rats and humans. Their research examined a wide array of different environmental otherwise unrelated compounds that were viewed as potential environmental 'contaminants,' wherein the authors hypothesized that short-term exposure to MDMA and other compounds was mitigated by a protective effect of specific ovarian cells (cumulus cells).

4.4.3 Genotoxicity

An Ames test of Ecstasy tablets with 0 to 57.5% MDMA, quantified by GC-MS, found no evidence of genotoxicity [382]. Micronuclear and chromosomal aberrance tests were performed in Chinese hamster ovary cells with MDMA purified from seized Ecstasy tablets and with N-nitroso-MDMA (N-MDMA), a putative metabolite of MDMA [383]. MDMA did not produce increases in either *in vitro* genotoxicity test.

4.4.4 Carcinogenicity

There are no preclinical findings directly addressing the carcinogenicity of MDMA. No tumors were reported after 28 days of daily MDMA administration in rats (0, 10, 50, 100 mg/kg) or dogs (0, 3, 9, 15 mg/kg) in a sponsor-supported preclinical study [378]. Gross pathology also failed to reveal any tumors in the rat after 13 days of repeated, increasing doses of MDMA (25-300 mg/kg) [380]. In the absence of positive results in genotoxicity tests, carcinogenic potential from intermittent dosing of limited number of exposures to MDMA in controlled settings is not of concern.

4.4.5 Reproductive and Developmental Toxicity

MDMA (15 mg/kg, s.c.) administered to pregnant rats was detected in amniotic fluid [384] indicating the potential for neonatal exposure. Preliminary teratological studies in rats (N=12 per dose) given 0, 2.5, or 10 mg/kg MDMA by gavage on alternate gestational days (GD) 6 to 18 found no abnormalities in gestational duration, litter size, neonatal birth weights, or birth defects (N=10 litters per dose), despite statistically significant reduction in maternal weight gain at 10 mg/kg [385]. These results are in contrast to physiological abnormalities resulting from prenatal methamphetamine and d-amphetamine exposure in mice and rabbits [386].

In a single-generation fertility and developmental toxicity study, C57BL/6 mice (N=25 per dose per gender) received a daily dose of 0, 1.25, 5, or 20 mg/kg MDMA via gavage [387]. Dosing for females spanned 2 weeks before mating through GD15 of pregnancy. Dosing for males spanned 4 weeks through the first day of pregnancy. There were no cases of MDMA-related mortality in females at all treatment levels. Gross necropsy of organs of MDMA-treated groups of male and female mice were unremarkable. No changes in copulation or fertility indices arose in MDMA-treated animals, but fewer pregnancies arose in all three MDMA-treated groups. When the fetuses were examined, no external, visceral, or skeletal malformations were detected in control or 1.25 mg/kg groups, but at 5 mg/kg (2 of 129) and 20 mg/kg (5 of 138) fetuses exhibited a cleft palate, anophthalmia, or skeletal malformations (short tail). Taken together, these studies suggest that MDMA has weak reproductive or developmental toxicity at high doses when MDMA exposure starts 2 weeks prior to mating and continues through GD15, which temporally covers ovulation through organogenesis and closure of the hard palate, in the females and spermatogenesis in the males.

In a separate perinatal/postnatal toxicity study done by the same researchers, C57BL/6 female mice (N=25) received a daily dose of 0, 1.25, 5, or 20 mg/kg MDMA via gavage daily from GD6 slightly after implantation through postnatal day (PND) 21 end of lactation [387]. Pup viability was assessed daily and gross external examination of pups occurred on PND 0, 4, 7, 14, 21, and 28. Behavioral and physical indices of development were observed in the F1 animals, such as pinnae detachment and righting reflex. Testes descent in males occurred on PND20 and vaginal opening occurred in selected females on PND30. Delivery and post-partum (nesting) behavior did not differ across treatment groups, and no MDMA-related differences in pup viability were detected, including pup survival rate and sex ratios per litter. No significant abnormalities were observed at necropsy of mice either found dead at lactation or killed at PND20. In contrast to the first study described above where MDMA was given 2 weeks before mating through GD15, when MDMA was given to only the females from GD6 to the end of lactation (both studies covered the period of organogenesis and closure of hard palate), there were no signs of impaired development and no significant differences in sexual development or reproductive capacity of F1 and F2 mice. This suggests that either dual exposure of male and female breeding pairs exacerbated reproductive toxicity, or possible evidence of a critical period for MDMA reproductive toxicity prior to organogenesis.

Male fertility after prenatal exposure was studied in male pups born to female Sprague-Dawley rats (N=6 per group) that received 0, 0.5, 5, or 10 mg/kg s.c. daily for three consecutive days per week for 10 weeks, including gestation and 3 weeks of lactation [388]. These females were mated with untreated males. The 5 mg/kg s.c. dose is two-fold greater than a human-equivalent dose based on plasma levels in other studies [86, 127, 132] and s.c dosing leads to higher plasma levels then dosing by gavage which was used in the studies above. There were no signs of toxicity in the 0.5 and 5 mg/kg groups, but dams in the 10 mg/kg group showed signs of sickness the week before delivery, and four of the six receiving 10 mg/kg and one of the five receiving 5 mg/kg were found dead at or prior to GD16. Mortality at 10 mg/kg s.c. indicates that this dose is too

high for use in reproductive toxicity studies; the authors subsequently discontinued the 10 mg/kg dose after week 10. Vestibular and motor function were assessed on PND21, with no differences between groups. Balano-preputial separation happened later than controls after 5 mg/kg in male pups on PND37-54. There were no differences in mating or fertility rate in F1 males. Hormone levels were similar across groups at PD81 and sperm morphology was unaffected. However, MDMA administration resulted in a significant higher incidence of DNA damage in Comet Test of sperm DNA at 5 mg/kg in relation to the control group. Minor dose-dependent alterations were seen in testicles, spleen and kidneys. There were no pathologies of the epididymis. Testicles showed a slight decrease in numbers of germ cells in 5 mg/kg treated rats.

A second study investigated male fertility after 0.5, 5 and 10 mg/kg administered s.c. once daily three times per week in rats (N=20 per group) for 12 weeks, covering puberty to onset of sexual maturity [389]. Ten rats per dose were mated with untreated females, with mating behavior alone serving as measure of reproductive function without reporting signs of conception. The other 10 rats per group were examined for testicular and sperm parameters, including sperm count and motility and morphology. There was a dose-dependent increase in tubular degeneration in testes in MDMA-treated rats, but sperm motility and morphology were unaffected. A 28-day repeated dose, sponsor-supported preclinical study, showed gross reductions in testicular size and microscopic evidence of testicular atrophy and prostatic enlargement. Mild testicular atrophy was observed microscopically in one of three dogs for the medium (9 mg/kg) and two of three dogs in the high (15 mg/kg) dose groups [378]. Prostatic enlargement was observed in two out of three dogs in the 15 mg/kg dose group. Thirteen days of repeated, increasing doses in the rat, starting at 25 mg/kg and ending at 300 mg/kg resulted in tubular atrophy in the testes of 3 of 20 rats [380]. When compared with sham-treatment or controls, testicular tissue from male rats that received daily injections of 5 or 10 mg/kg MDMA for 16 days exhibited increases in heat shock protein 70 (HSP70) and signs of apoptotic cells [390]. Taken together, these studies suggest minimal male fertility toxicity at human-equivalent doses, with signs of increased toxicity at higher doses.

In an initial developmental toxicity study, pregnant rats were administered twice-daily injections of high doses of MDMA (15 mg/kg) or saline from embryonic days (E) 14 to 20. Rat pups that had received MDMA showed reductions in the dopamine metabolite homovanillic acid, along with reductions in the serotonin metabolite 5-HIAA. Prenatally exposed MDMA animals also had reduced dopamine and serotonin turnover in the nucleus accumbens [391]. The same team reported postnatal exposure to MDMA correlated with reductions in serotonin and its metabolite, as well as significant increases in dopamine turnover and the prevalence of a dopamine metabolite in multiple forebrain structures and the brainstem. BDNF was significantly increased (19% to 38%) in all forebrain structures and in the brainstem in MDMA-exposed neonates [392]. The researchers proposed that the increase in BDNF was compensating to minimize MDMA effects. However, later studies found that neonatal MDMA exposure did not affect hippocampal concentrations of serotonin or dopamine [393] and that enhanced BDNF detected in the occipital lobe did not mediate the abnormal serotonergic signaling observed following neonatal MDMA exposure [394]. PND 11 and 20 were proposed to be equivalent to the third trimester of gestation in humans [392], so it is possible that exposure to high doses of MDMA *in utero* could have developmental effects, but these do not appear to be related to BDNF levels. The doses used in the rat studies are approximately eight to 10 times greater than a human equivalent dose.

Prenatal MDMA exposure at high doses significantly increased locomotor activity of rat pups in a 20-minute novel cage environment test [391]. Rodents treated with MDMA during development were not significantly different than rodents who received MDMA as adults. The results of several behavioral tests indicate that developmental MDMA exposure combined with adult exposure may interfere with some aspects of learning, including visual-spatial memory and time spent with a novel object [393]. Neonatal MDMA administration did not alter working memory

in the object-recognition test in young adulthood (PD 68 to 73) and there were no differences in binding of the radiolabeled selective serotonin reuptake inhibitors (SSRI) citalopram to the SERT at this age. However, the pretreated animals showed increased thermal dysregulation and serotonin syndrome responses following MDMA challenge, especially with respect to head-weaving stereotypy [395]. Another team also found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA [396]. A study in neonatal rats suggests two distinct critical periods wherein repeated doses affected learning versus acoustic startle [397]. Serotonergic factors may be involved in the developmental effects of MDMA, with the SSRI citalopram producing similar learning impairments in neonatally exposed rats [398]. Given differences between human and rodent development and thermoregulation, it is not clear whether such findings can be generalized to humans (see Section 4.2.2.3 Thermoregulatory Effects in Animals).

Previous research supported a possible link between Ecstasy use and birth defects [399], while an epidemiological study of a large cohort of pregnant women in England conducted in 2004 failed to support this link, at least in respect to a specific cardiac defect [400]. However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using Ecstasy when they learn they are pregnant [401]. A 2012 survey of 96 women in the UK interviewed about their drug use during pregnancy found a link between self-reported extent of prenatal MDMA exposure and delays in infant development at 12 months, with heavily exposed infants delayed in mental and motor development, but not language or emotional development [402]. These results were repeated in a 2016 survey of 96 mothers who reported heavier MDMA use (1.3±1.4 tablets per week) during pregnancy. Infants had motor delays from 4 months to 2 years of age that were not attributable to other drug or lifestyle factors [403]. Since there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA in clinical trials. None of the sponsor's studies enroll pregnant or lactating participants .

4.4.6 Hyperthermia

At least one case series of individuals seen on the same night and near or in the same nightclub suggest a relationship between Ecstasy dose and likelihood of hyperthermia [404]. A case report and some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans [285, 286]. When assessing acute effects of Ecstasy, hyperthermia is one of the more frequently reported acute harms of Ecstasy [61, 282].

A study of rats receiving subcutaneous injections of 9 mg/kg MDMA, just under half the LD50 of 20 mg/kg in rats housed together, reliably produced malignant hyperthermia in the context of warm ambient temperatures of 29°C and during social interaction [210]. At this dose, MDMA monotonically increased intracerebral heat production and muscle temperature while causing strong and sustained peripheral vasoconstriction, which inhibits heat dissipation. Social interaction on its own also induced metabolic brain activation and transient vasoconstriction in rats, which compounds the hyperthermic effects of MDMA observed at toxic doses and warm ambient temperatures. These effects are likely to be mediated through dopaminergic pathways [405, 406], which have been shown to play a minor role in producing the effects of MDMA in humans [36].

4.4.7 Cardiovascular Toxicity

Injections of 20 mg/kg MDMA in conscious rats assessed by radio telemetry (10.7 times the equivalent dose in humans) found that MDMA caused a prolonged increase in blood pressure [226]. In the same study, MDMA was found to produce mild isotonic contractions of aorta and vas deferens vascular tissue in anesthetized rats, but could also inhibit prejunctional contractions evoked by stimulation [226]. In-vitro work in human internal mammary artery suggests that contractile effects may increase at high temperatures (40ºC versus 37ºC) and that some metabolites may contribute to this effect [407].

The elevation of blood pressure and increased heart rate produced by MDMA, similar to that produced by other sympathomimetic drugs, can lead to additional risks and complications [408-410], such as stroke, cardiac events, or other cerebrovascular events, including cerebral venous sinus thrombosis [411] and cerebral or subarachnoid hemorrhage [88, 412-416]. In two such cases, a previously existing underlying arteriovenous malformation appeared to play a role in the event [412, 414]. Intra-cardiac pressures, intra-arterial pressures, angiotensin II, pain, and adrenergic (α_2) central nervous stimuli can also influence AVP secretion [417]. Increased AVP concentration is described in several studies as a strong predictor of mortality in patients with chronic heart failure and acute heart failure, and contributes to increases in blood pressure [418]. As with any amphetamine, increased heart rate (tachycardia) and elevated blood pressure can also lead to cardiac events, such as arrhythmias or myocardial infarction [419, 420]. Fatal dysrhythmias have been reported following heavy MDMA use, resulting in ventricular fibrillation and asystole. Individuals with underlying cardiac and/or pulmonary disease and preexisting conditions such as Wolff-Parkinson-White syndrome are especially at risk for heart failure and fatal arrhythmias. Although the presence of MDMA was rarely confirmed in reported cases, these types of events are all well-established complications of hypertension and can occur after use of amphetamines. There have been no such events to date in any clinical trial of MDMA.

Some researchers have expressed concern that MDMA activity at $5HT_{2B}$ receptors might be indicative of increasing risk of valvular heart disease with repeated use [24]. Studies in Ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential VHD [287], and a case of VHD has occurred in a man reporting approximately 16 years of heavy Ecstasy use, from age 17 to 33 years old. [421]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Echocardiographic readings in eight Ecstasy users also failed to find any cardiac abnormalities [52]. Since VHD-associated changes and VHD only occurred after extremely heavy Ecstasy use, they are unlikely to be a risk within the research or therapeutic context.

4.4.8 Hyponatremia

A number of case reports describe hyponatremia after uncontrolled, non-medical Ecstasy use [62, 422-424]. A recent meta-analysis showed that a moderate reduction of serum sodium concentration is associated with an increased risk of death in different pathologic conditions [425]. Relationships have been found between reduced plasma sodium, a measure of hyponatremia, and variations in COMT and CYP2D6 genotypes, possibly related to increased AVP and oxytocin release associated with MDMA [292]. Active doses of MDMA likely inhibit CYP2D6 in most individuals, as described in Section 5.2.1 Pharmacokinetics. Behavioral factors, including vigorous exercise and excessive consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones AVP and oxytocin, likely all contribute to this very rare but serious condition in Ecstasy users [32]. Women are generally more likely to exhibit hyponatremia than men [426, 427], including Ecstasy or MDMA related hyponatremia [62]. Heart failure is commonly associated with hyponatremia, and is also characterized by

increased concentrations of AVP [428-430]. Hyponatremia has not occurred during a controlled clinical trial with MDMA.

4.4.9 Hepatotoxicity

In vitro studies and studies employing high, repeated doses of MDMA, estimated as being at least five times greater than expected in a clinical trial [431], report damage to liver cells [432-434]. A study looking at metabolites produced by mouse primary hepatocytes (liver cells) after exposure to high doses of MDMA (up to 0.427 mM, or 427 µM) reported intracellular and extracellular metabolites involved in several processes, including fatty acid and glutamate metabolism, and antioxidant defenses [435]. An *in vitro* study performed on a human liver cell line (HepG2) comparing cytotoxicity of MDMA with methamphetamine and related phenethylamines and ketones reported elevation in some markers of cytotoxicity considered 'moderate' [436]. These effects were seen when cells were bathed in at least 16 µM MDMA for 72 hours. Though many of these studies employed MDMA concentrations much higher than would occur after human ingestion, there are reports of liver disease in Ecstasy users. Studies in rats suggest a role of body temperature in promoting liver toxicity. A review of the literature highlights many potential factors, including body temperature and metabolism in preclinical studies and polydrug use, including alcohol, and environmental factors in humans [437]. Due to disparities in dosing and method, it is hard to establish whether these findings are relevant for liver toxicity in human Ecstasy users.

Hepatotoxicity (liver disease or damage) was reported in approximately 16% of 199 case reports from Ecstasy users in non-medical, uncontrolled settings, collected from the mid-1990s to 2001, making it the third most common serious adverse report in the literature. There appears to be more than one pattern of Ecstasy-related hepatotoxicity, and several factors, including polydrug use and setting of use may be involved [437]. Acute liver failure or hepatitis has occurred after reported ingestion of a single Ecstasy tablet [438-441]. In other cases, human hepatotoxicity has occurred after months of regular Ecstasy use [442]. Standard toxicity studies failed to find liver damage after MDMA administration in rats or dogs after 28 days of exposure [378]. A 13-day, repeated daily dosing study showed significant elevations of the liver toxicity markers alanine aminotransferase (ALT) and aspartate transaminase (AST) in male rats, suggesting potential liver toxicity in this sex. Despite a rise in these markers, gross pathology and microscopy of liver tissue failed to show any liver damage. [380] No cases of liver disease have arisen during controlled studies in humans. Examinations of case reports and a number of *in vitro* studies suggest an association between hyperthermia and hepatotoxicity. However, liver disease also occurred in some individuals without the occurrence of hyperthermia, appearing after continued use and resolving after abstinence. These reports suggest a potential immunological mechanism. Since hepatotoxicity has been noted in Ecstasy users, *in vitro* and *in vivo* studies have examined the hepatotoxicity of MDMA. These studies show that high repeated doses of MDMA can impair liver cell viability *in vivo* [432], and can increase profibrogenic activity in cultured stellate cells [434] while reducing cell viability without producing lipid peroxidation *in vitro* [432, 443]. At higher ambient temperatures, a toxic dosing regimen was capable of increasing lipid peroxidation and activating apoptosis due to oxidative stress [444]. A single intraperitoneal dose of 20 mg/kg in rats was still capable of disrupting glutathione homeostasis, decreasing antioxidant enzyme activity, and lipoperoxidation activating apoptosis in one study [445]. However, peak liver exposure to MDMA in sponsor-supported studies should be approximately one-eleventh the concentration shown to impair cell viability in these studies. No cases of liver disease or hepatotoxicity have occurred in controlled clinical trials with MDMA. See Section 5.3.6 Hepatic Effects for discussion of liver panel results in sponsor-supported clinical trials.

4.4.10 Neurotoxicity

Repeated very high doses of MDMA in animals reduce total serotonin levels in the brain, impair transport of serotonin, and cause psycho-behavioral changes such as increased anxiety [137, 258, 446-448]. In combination with other drugs or in high dose binge administration studies, MDMA may provoke serotonin syndrome. For example, rodents respond to high doses of MDMA by exhibiting flat body posture, forepaw treading and an erect tail ("Straub tail") [448]. These behaviors are considered indicators of serotonin syndrome. Doses used in most preclinical studies of neurotoxicity are at least five times the amount used in clinical trials or nonmedical settings and can be as high as 20 times that amount.

Studies in rodents and primates suggest that repeated high doses of MDMA could reduce regional serotonin, damage serotonin axons and cause neurotoxicity [137, 149, 449-452] and promote apoptosis in the hippocampus after 5 or 10 mg/kg MDMA given daily for 1 week [239]. In contrast, a study in monkeys given intermittent periodic doses closer to human equivalent doses in milligrams per kilogram reported reduced maturation of hippocampal cells without detecting signs of apoptosis [240]. However, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses, with findings now clearly indicating that doses used in nearly all rat and most primate studies are inappropriately high for comparison to use in clinical settings and are more pertinent toxicological effects of MDMA [86, 127, 132].

In a 13-day toxicity study, using repeated and increasing dosing, ranging from 25 mg/kg to 300 mg/kg caused no changes in the brain tissue of treated rats compared to controls [380]. A 28-day repeated dose, toxicity study in the rat showed vacuolar changes in the brainstem adjacent to the trigeminal nuclei in one of ten animals receiving 50 mg/kg of MDMA and similar lesions in five of ten animals receiving 100 mg/kg. [379] Lesions were also observed in the CNS of MDMA-treated dogs in an identical toxicology study with doses of 3, 9 and 15 mg/kg, however the presence of the lesions was not dose-dependent, suggesting that they could be background events. These lesions included white matter changes, neural malacia and cellular infiltrates of the cerebrum. Neural chromatolysis was observed in the brainstem. The pathogenesis of these changes is unknown. Another sponsor-supported study of male Sprague-Dawley rats using 40 mg/kg and 80 mg/kg twice a day for four days did not produce any morphological brain changes but found a reduction in serotonin (5-HT) and 5-Hydroyindoleacetic acid (5-HIAA) at both dosing levels [379].

Research conducted from 2018 to 2019 has focused on hypothesized contributing factors involved in MDMA neurotoxicity. Autophagy, a means of addressing dysfunctional organelles or abnormal proteins that are considered a marker of environmental stress. In vitro studies with mouse brainstem tissue that exposed cells to high doses of MDMA (100 to 1000 µM) for 24, 48 or 72 hours and using immunoassays detected signs of autophagy after 1000 µM at 24 hours and 500 µM after 72 hours [453]. An in vivo study in rats that received twice-daily doses of 10 mg/kg MDMA for four consecutive days. MDMA increased signs of autophagy in dorsal raphe and reduced indicators of brain serotonin transporter, while inhibiting autophagy attenuated reduction in SERT markers [454]. Reducing autophagy also reduced corticosterone release and reduction in activity during the "forced swim" test, considered a rodent model of antidepressant action, with more time spent swimming a sign of antidepressant drug activity. The authors consider these findings a demonstration that autophagy plays a key role in MDMA neurotoxicity. These studies do not address whether these processes occur in humans, or during lower, less intensive dose regimens.

A study in mice looked at neurons stained for nitric oxide synthase (NOS), hypothesized to be involved in MDMA neurotoxicity. Mice in this study were given an intensive repeated-dose

regimen of 14, 28 or 36 administrations of 10 mg/kg MDMA twice daily, and an increase in NOS-positive neurons was seen after the two higher dose regimens up to three months after drug administration [455]. Another mouse model of neurotoxicity involved administering 1 mg/kg MDMA daily for three months, using a human-equivalent dose in an unusually intensive regimen very dissimilar to clinical use [456]. This study reported apoptosis (a type of cell death) in retinal cells, reduced retinal function and markers of increased oxidative stress. This last study is the first to assess toxicity in retinal cells. Since there is, to date, only a single report of retinal damage occurring after Ecstasy use in a case without reporting any detectable MDMA, there is little evidence for this being a common or significant issue.

Most studies suggested that heavy but not moderate Ecstasy users had impaired verbal memory and lower numbers of estimated SERT sites, assessed via imaging with radioactively labeled ligands in positron emission tomography (PET) or single photon emission tomography (SPECT), with heavy use often defined as 50 or more times or tablets. Taken together, findings from these studies suggest there is some risk of long-term effects in heavy Ecstasy users with respect to number of estimated SERT sites in specific brain areas and performance on measures of memory. However, interpreting findings of changes in serotonin receptors or cognitive function after repeated Ecstasy use are complicated by the possible impact of polydrug use and other potential pre-existing factors in retrospective reports, and the findings are not readily transferrable to use of MDMA in a therapeutic or research context.

Many investigations have examined cognitive function in Ecstasy users with the goal of demonstrating long-term effects of purported neurotoxicity of Ecstasy. Rogers and colleagues performed a meta-analysis on a large number of retrospective studies of Ecstasy users and various cognitive functions. Given methodological flaws in this type of analysis, the investigators cautiously concluded that there might be a significant effect of Ecstasy use on verbal memory, and a lesser effect on visual memory [61].

Retrospective designs and inappropriately matched samples continue to appear in the literature [457-459], even when using multiple control groups. Two meta-analyses of memory in Ecstasy users arrived at somewhat contradictory conclusions [460, 461]. Both detected an association between Ecstasy use and impaired performance on at least some measures of memory. However, one reported that this association had a medium to large effect size with no effect of Ecstasy dose [460], while the other reported that the association had a small to medium effect size with an Ecstasy dose effect, and that polydrug use itself contributed to impaired cognitive function [461].

A meta-analysis comparing current Ecstasy users and drug-using controls on visuospatial skills reported that current users performed less well on measures of visual recall, recognition and item production than controls [462], but found no significant relationship between lifetime Ecstasy use and visuospatial task performance. A longitudinal study comparing people who continued to use Ecstasy with those who did not do so detected lower performance on immediate and delayed visual memory [463]. In a second follow-up in the same sample reported lower scores in visual memory, at marginal significance and no further impairment [464]. An examination of the relationship between elements of Ecstasy use history and verbal memory reported that use in the past year, especially in men, was associated with impaired verbal memory [465]. The authors suggest that gender differences in polydrug use may be involved.

A study comparing performance on a test of verbal memory in 65 Ecstasy users enrolled in clinical trials of MDMA and an equal number of age and gender matched non-drug using controls from other trials failed to detect significant differences between the two groups [466]. This study employed a pre-determined measure of clinical significance, 1.5 times the average standard deviation of the healthy controls and used a Bayesian statistical test suited for assessing a null

hypothesis. It is notable that none of the participants were enrolled in studies designed to compare cognitive function in ecstasy users, which may have reduced anxiety and potential risk of "stereotype threat" that may be faced by substance users completing assessments of cognitive function, which was done to reduce expectancy in the study [467].

The nature and strength of the association between regular Ecstasy use and any impairments in executive function remains inconclusive, with studies reporting conflicting results [5, 298, 299, 468, 469]. Findings from a study published in 2014 did not find differences in multitasking [345]. A meta-analysis comparing executive function in Ecstasy users and non-Ecstasy using controls found a significant effect of Ecstasy use on one component of executive function (updating), no effect on another (shifting) and mixed results when looking at other components (response inhibition and access to long-term memory) [470]. Polydrug use likely contributes to findings of impaired executive function seen in Ecstasy users [334, 471]. Current research has not settled the question.

Psychiatric problems after uncontrolled, non-medical Ecstasy use were reported in 22.1% of 199 case reports from the early 1990s to 2001, and are the most common reason for appearance at an emergency department [422]. Psychiatric symptoms included affective responses, such as dysphoria, anxiety, panic, and psychotic response, as well as cases with mixed psychotic and affective features. The most common problem reported included panic, restlessness and psychotic response, as seen a systematic review and several epidemiological case series [61, 472]. The mechanisms behind Ecstasy-associated psychiatric problems remain unclear, but are likely the result of an interaction between pharmacology and individual susceptibility. The difficulty of assessing the frequency of these events is increased given that pre-existing psychiatric problems occur in people who choose to use Ecstasy [473] and findings of an association between use of Ecstasy and other drugs and self-reported symptoms of anxiety and depression. As described earlier, most cases of psychological distress after Ecstasy use resolved after supportive care [60, 63]. Anxiety responses associated with MDMA administration reported in controlled trials have resolved over time, usually either during the period of acute drug effect or with the waning of drug effects.

4.5 Serious Reports of Incidents, Mortality, and Morbidity in Animals and Epidemiological Settings

Intravenous MDMA doses that cause lethality in 50% of the cases, known as the LD50, are 97 mg/kg in mice, 49 mg/kg in rats, 14 to 18 mg/kg in dogs, and 22 mg/kg in monkeys [117]. LD50 may vary across strains, sexes, and housing conditions [474-476]. For example, LD50 in mice housed together is 20 mg/kg, which is considerably lower than in isolated animals [212, 477]. Reducing ambient temperature and administering the $5HT_{2A}$ antagonist ketanserin reduced lethality, suggesting that amplified elevation in body temperature and activity at serotonin receptors may promote lethality in group-housed mice given MDMA [212]. Considerable variation across studies in environmental factors, that are often underspecified in published reports, contribute to challenges in extrapolating findings in animal studies that may be relevant in epidemiological settings.

Numerous serious events, including fatalities, have been reported in humans after Ecstasy use in unsupervised and uncontrolled settings. These events are relatively rare given the prevalence of Ecstasy use [57, 58]. These include hyperthermia (potentially arising from "serotonin syndrome"), psychiatric problems, hepatotoxicity (secondary to hyperthermia), cardiac disorders and hyponatremia [57, 60-62, 478]. Set and setting likely play a role in the development of some Ecstasy-related AEs, such as vigorous exercise, lack of attention to somatic cues, and too little or too much hydration combined with pharmacological action on AVP resulting in hyperthermia or

hyponatremia [59, 424]. Even if ambient temperature does less to moderate the effects of MDMA on body temperature than originally believed based on animal studies, other environmental and behavioral factors, as those related to vigorous exercise, may be involved. It is important to note that not all reports of AEs in Ecstasy users provide information on whether MDMA was detected in plasma or other fluids, with some relying on self-report or the reports of friends as to identity of substances consumed. Reports indicating detectable MDMA will thus be the best indicators of an actual association. Unexpected SARs have not occurred in any of the human MDMA research studies thus far.

While case reports do not provide an appropriate basis for estimating the relative frequency of these events, they can provide information on the possibility of an event occurring. Most Ecstasy-related emergency department admissions are the result of people experiencing anxiety or panic reactions after use and involve supportive care only [60, 63, 479]. An extensive systematic review reached similar conclusions concerning the frequency and nature of emergency department admissions, though also noting that owing to complexities of nonmedical and recreational use, the researchers found it hard to establish a lethal dose [61]. However, a pair of case series drawn from two different events suggests a general relationship between estimated dose and number of emergency department admissions after exhibiting seizures, unresponsiveness or hyperthermia, with both series reporting high doses of MDMA (230 and 270 mg) in sample tablets or capsules [480, 481]. As is the case with fatalities associated with reports of Ecstasy use, medical emergencies after Ecstasy use are more likely to occur in men [60]. Individuals consuming Ecstasy with pre-existing conditions are at increased risk when consuming drugs of unknown purity, identity, and dose in uncontrolled settings.

Table 2: Summary of Published Morbidity and Mortality Reports

Body System	Reports	Morbidity Reports	Mortality Reports	Total Reports
Thermoregulatory Disorders (MedDRA "Body Temperature Conditions" under "General Disorders and Administration Site Conditions)	Hyperthermia, Hyperprexia, (sequelae incl. Rhabdomyolysis, seizure, Hypoglycemia)	137 [88, 480, 482-498]	46 [88, 243, 480, 482, 494, 499, 500] [501, 502]	183
Cardiac Disorders	Cardiac valve disease, Ventricular fibrillation, Cardiac arrest, Arrythmia, Myocardial infarction, Generalized tonic-clonic seizure, Acute coronary syndrome, Myocardial necrosis,	15 [420, 421, 503-509]	12 [419, 482, 510-514]	27

	Cardio-respiratory arrest, Cardiomyopathy			
Osmoregulatory Disorders (MedDRA 17.1 "Electrolyte and fluid balance conditions" under "Metabolism and Nutrition Disorders"	, SIADH, Urinary retention, Hyponatremia, (sequelae of cerebral oedema, Acute renal failure)	19 [515-527] [528]	6 [420, 529-533]	25
Metabolism and Nutrition disorders	Diabetic ketoacidosis (MDMA+alcohol)	0	1 [534]	1
Hepatobiliary Disorders	Acute fulminant hepatitis, Liver disease, (Sequelae: Disseminated intravascular coagulation)	4 [441, 509, 535, 536]	5 [537-541]	9
Blood and Lymphatic System Disorders	Aplastic anemia	3 [542, 543]	1 [544]	4
Injuries, Poisonings, and Procedural Complications	Anaphylactic shock, Facial rash eruption, swollen lip (allergic or mechanical injury)	2 [545, 546]	1 [547]	3
Nervous System Disorders	Hemorrhage, Infarct, Hippocampal sclerosis (suspected), Encephalopathy, Leukoencephalo -pathy Amnestic syndrome	15 [408, 409, 548-557]	0	15
Dental And Gingival (under "Gastrointestional Disorders"	Xerostomia, Bruxism, Dental erosion	15 [558-560]	0	15

Psychiatric Disorders	Psychotic episode, Depressive episode, Obsessive-compulsive disorder, Auto-enucleation	4 [561-563]	0	4
Respiratory, Thoracic, and Mediastinal Disorders	Subcutaneous Pneumomediastinum, Epidural pneumatosis, Diffuse alveolar hemorrhage, Asthma Airway necrosis	9 [419, 564-571]	1 [572]	10
Eye Disorders	Lagophthalmos, Keratopathy, Bilateral sixth nerve palsy	4 [573, 574]	0	4
Injuries, Poisonings, and Procedural Complications	Unknown cause of death Heat stroke*	0	207 [419, 575] [576]	207
Skin and Subcutaneous Tissue Disorders	Angioedema	1 [577]	0	1
Vascular disorders	Ischemia in person with myocardial bridging	0	1 [578]	1
Total Reports		500	279	679

*MDMA detected in blood of three fatalities but authors viewed as heat stroke resulting from combination of environmental condition (outdoor music festival in tropical climate) combined with drug use.

Five hundred case reports of morbidity and 279 reports of morbidity associated with Ecstasy use from 1986 through 2018 are summarized in Table 2. Of these 279, 32 were described in a cumulative 2002 literature review with incomplete citations of sources, and are conservatively reported in addition to individual case reports of morbidities in the literature [482]. Detectable levels of MDMA in blood or urine are reported in less than half of these case reports, and range from 50 ng/mL (reported as less than 0.05 mg/L) in the case of anaphylactic shock [547] to 1500 ng/mL (reported as 1.5 mg/L) in a fatal case of hyperthermia and rhabdomyolysis [500].

Assessment of brain and blood MDMA in 11 fatalities under forensic autopsy detected lower doses in deaths where MDMA was determined to be incidental (accident, homicide) or detected in combination with other drugs versus blood and brain levels in a pair of deaths where cause of death was MDMA and no other drugs [579]. It is more difficult to associate events with MDMA when the compound is not detected or when detection is for amphetamines in general. Some events, such as VHD, acute hepatitis with gallbladder inflammation, liver disease, or urinary retention occurred in individuals who self-reported daily use for months to years prior to the

event. In the majority of the 202 poisoning cases with unknown cause of death in the UK and Wales between 1996 and 2002, Ecstasy was used in combination with opiates [575]. Polysubstance use is common in the majority of serious reports presented.

Thermoregulatory disorders play a part in the development of a constellation of disorders across body systems described below. Primary symptoms are hyperthermia resulting in rhabdomyolysis described in 137 reports of morbidity and 46 reports of mortality, constituting the most common acute adverse effect associated with Ecstasy. Sympathomimetic effects of MDMA, at unknown doses and purity, in combination with permissive factors in uncontrolled settings, can lead to serious reports of acute and persisting adverse effects on multiple organs. In research settings, the risk of hyperthermia is limited by controlling ambient temperature, conducting treatment sessions in relaxed, private environments, and generally limiting permissive factors.

Cardiac disorders associated with Ecstasy in the context of hyperthermia resulted in 15 reports of morbidity and 12 reports of mortality. Several fatal cases of cardiac arrest were reported. In addition, a non-fatal cardiac arrest occurred in the context of a genetic arrhythmia disorder, catecholaminergic polymorphic ventricular tachycardia [504]. Apparent use of Ecstasy, with concurrent use of other amphetamines during pregnancy, was associated with seizures and myocardial infarction [507, 508]. As evidenced by these reports, individuals consuming Ecstasy with pre-existing conditions that can influence cardiovascular and cardiac function are at increased risk when consuming drugs of unknown purity, identity, and dose in uncontrolled settings.

Osmoregulatory disorders associated with Ecstasy in the context of hyperthermia resulted in 19 reports of morbidity and six reports of mortality, with acute renal failure (ARF) as the most common cause of death. As described in Section 4.4.8 Hyponatremia, increased AVP secretion caused by MDMA in combination with permissive factors in uncontrolled settings can lead to serious reports of acute and persisting adverse effects on multiple organs, including the liver. Individuals consuming Ecstasy with pre-existing conditions that can influence renal function are at increased risk. In response to this risk, many users tend to overcompensate with excessive consumption of water, leading to dilutional hyponatremia. Prevention of hyponatremia with limited consumption of electrolyte containing fluids and controlled ambient temperatures are required to preserve the body's homeostatic maintenance of fluid balance.

Metabolism and nutrition disorders associated with Ecstasy has resulted in one report of mortality. A patient with Insulin-dependent diabetes mellitus consumed alcohol and Ecstasy which caused diabetic ketoacidosis [534]. An autopsy revealed microhemorrhages in the brain with subnuclear vacuolization and Armanni-Ebstein changes in renal tubes. A low level of MDMA was found in the blood (<0.01 mg/L).

Hepatobiliary disorders associated with Ecstasy use resulted in four reports of morbidity and five reports of mortality. One of the mortality reports happened 1 week after Ecstasy use and was consistent with acute fulminant hepatitis in the absence of viral infection. This patient died despite liver transplantation efforts [537]. Typically, mortality results from disseminated intravascular coagulation (DIC) caused by platelet dysfunction associated with liver failure. Non-fatal morbidity reports range from acute hepatitis associated with daily usage of five to eight tablets of Ecstasy for 3 months in combination with alcohol [535] to liver damage in combination with congestive cardiomyopathy [509]. Given that polysubstance use and prior insult to liver function cannot be ruled out, the frequency of isolated serious hepatotoxicity cases in the absence of hyperthermia are rare among serious reports associated with Ecstasy use. Hepatotoxicity is more common among serious reports in combination with hyperthermia and acute renal failure.

Blood and lymphatic system disorders associated with Ecstasy use resulted in three morbidity reports and one mortality report of aplastic anemia. The death after aplastic anemia occurred from complications of immunosuppressant therapy followed by an allogenic stem cell transplant, 17 months after the first admission [544]. The patient had initially presented with progressive weakness and epistaxis, resulting from daily Ecstasy use for 7 months, combined with heavy alcohol intake. Further examination revealed the replacement of bone marrow tissue with fatty deposits, likely due to alcohol consumption and exacerbated by chronic Ecstasy use. Three reports of morbidity ranged in prior Ecstasy use levels from once to four times in the prior year, with two cases spontaneously resolving within 2 months and the treated case failing immunosuppressive therapy and recovering 4 months after subsequent bone marrow transplant [544].

A report of possible anaphylactic shock and subsequent death occurred in a 13-year old girl who had at least one previous exposure to Ecstasy [547]. Her friends reported that she experienced swelling lips after her first exposure. After approximately 1.5 tablets, the girl experienced nausea and vomited, and later had difficulty breathing. On admission she was hypothermic and hypotensive. A low level of MDMA (<0.5 mg/dL) was detected in blood. None of the other individuals consuming tablets from the same batch underwent similar experiences. Autopsy found a massive brain edema as well as laryngeal oedema and lung congestion. Chemical analyses ruled out hyponatremia. The reaction may have been to MDMA or to an adulterant in the tablet. The authors of the report do not report whether tablets were assessed for contents. A report of swollen lips in a woman with detectable levels of MDMA in blood (1.466 mg/L) is ambiguous as to cause of swelling, since the patient may have experienced a sexual assault and injuries in transit to ER, and cannot clearly be established as an allergic reaction [546].

Nervous System disorders associated with Ecstasy use resulted in 15 morbidity reports and no mortality reports. Memory difficulties arising immediately after Ecstasy use have been reported in a sporadic user [552]. The memory difficulties arose in a man reporting use of Ecstasy five or six times, with confusion and cognitive impairment reportedly occurring after taking a single tablet at a party. Cognitive function was assessed 7 years later. Imaging showed signs of hippocampal sclerosis. It is not clear from the report whether the individual used Ecstasy prior to or after this event. The individual had hypertension, raising questions concerning possibility of a cerebrovascular event. In a report of a serious neurological event with 0.83 ng/mL MDMA detected in the hair of a girl who developed encephalopathy [551] during chronic low or moderate Ecstasy use, cognitive function and memory problems associated with neurological damage was reported. Upon cessation of use 16 months later, extensive hippocampal remodeling was reported assessed through PET scans. This finding is consistent with hippocampal dendritic spine remodeling observed in rats receiving 20 mg/kg MDMA for four days intended to simulate chronic usage in humans [580], however, the clinical presentation was also similar to CNS herpes infection, so it is difficult to attribute this isolated case report to only Ecstasy use. Two reports have identified bilateral lesions in the globus pallidus of ecstasy users during magnetic resonance imaging (MRI) or autopsy, with a third report finding hippocampal changes in imaging associated with amnestic syndrome [553-555]. Due to the retrospective and infrequent nature of these reports, it is difficult to determine causality.

Respiratory, thoracic, and mediastinal disorders resulted in 9 reports of morbidity and one report of mortality in the context of Ecstasy use. A single mortality report of airway necrosis occurred in a 25-year-old male who had a history of occasional Ecstasy use by inhalation. The patient was initially found unresponsive and was resuscitated, but airway necrosis due to vasoconstriction of airway walls led to hypoxic cardiac arrest [572]. This report is not consistent with the usual respiratory, thoracic, and mediastinal SARs reported from oral administration of Ecstasy. The mortality report is likely due to the patient's chosen route of administration.

Overall, the risks of serious events appear to be minimal in controlled settings with adequate screening with eligibility criteria defined in study protocols. None of these events have occurred within the context of human clinical studies with MDMA.

4.6 Abuse Potential in Nonclinical Studies

Nonclinical studies support that MDMA possesses abuse potential, but much less than amphetamine. A number of studies have investigated the abuse liability of MDMA in animals through paradigms of drug seeking, drug discrimination, and withdrawal. Mice, rats, and monkeys self-administer MDMA, indicating that MDMA has rewarding properties in animals [581-584]; however, the rate and response-acquisition of self-administration is much lower than other drugs of abuse, such as cocaine or heroin. Rodent studies found that training attempts at self-administration required an increased training dose of 1.75 mg/kg for acquisition over a five-week period [583, 585-587]. Research that used rate of self-administered intracranial self-administration (ICSS) as a measure of abuse liability, and comparing response to 0.32, 1, or 3.2 and 3 mg/kg MDMA in male and female rats reported that MDMA increased responding for ICSS when the rate of responding for ICSS was low, and reduced seeking ICSS when rate of responding was very high in both sexes [157].

Physical dependence and drug withdrawal were investigated by treating mice with 10 mg/kg i.p. MDMA twice daily for five days. When compared with rats trained to self-administer cocaine, MDMA-trained rats were less likely to return to self-administration after a period of abstinence [582]. Results showed that mice did not exhibit aversive/dysphoric or anxiogenic behaviors after treatment, indicating that high doses of MDMA do not induce classical symptoms of physical dependence [588]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [581], but typically reduce their MDMA intake over time. While monkeys work hard to obtain MDMA, they work harder to obtain other psychostimulants, such as cocaine or methamphetamine [586, 587]. Taken together, results in animals suggest that the abuse liability of MDMA is low to moderate.

Nonclinical drug discrimination studies investigating the discriminative stimulus effects of MDMA as either hallucinogenic or stimulant have reported inconsistent findings, indicating that psychoactive effects of MDMA are not expressly hallucinogenic or stimulating [589]. Two-way discrimination studies with MDMA are not specific enough to assess the complex pharmacological profile of MDMA and lead to low accuracy and mixed results. In three-way discrimination studies, MDMA has discriminative stimulus effects that are more serotonergic, with minimal involvement of dopamine. One such study found that lysergic acid diethylamide (LSD) produced dose-dependent increased substitution for MDMA while neither cocaine nor 2,5-dimethoxy-4-bromoamphetamine (DOB) substituted for it [590].

Administering MDMA to amphetamine-trained rats suggests that dopamine plays a role in stimulus properties, but blocking serotonin receptors interfered with recognizing MDMA, while administering dopamine receptor antagonists did not do so [180]. A higher dose of 3 mg/kg may have a greater dopaminergic component, while 1.5 mg/kg may have more of a serotonergic component [179] in drug discrimination studies in rats. Serotonin $5HT_{1A}$-acting drugs were treated similarly to both 1.5 mg/kg and 3 mg/kg MDMA [179]. Drug discrimination studies in SERT knockout rats supports a key role for serotonin release in producing the subjective effects of 1.5 mg/kg MDMA [591]. The ratio of serotonin to dopamine release are likely to influence stimulus characteristics of MDMA in animal models, and these studies lead to the definition of a unique class of drugs called the Entactogens, which are clearly distinguishable from hallucinogens and stimulants. Discrimination research in a sample of monkeys trained to

discriminate cocaine from saline and tested with cathinones, amphetamines, and MDMA and MDA, suggested that the greater serotonergic effects of MDMA are at least partially related to the methylenedioxy structure [592].

Features of Ecstasy abuse and dependence in humans are consistent with preclinical findings in self-administration studies of moderate abuse liability that is greater than that for serotonergic hallucinogens, but less than that for stimulants [583, 593].

5.0 Effects in Humans in Clinical Settings

5.1 History of Use in Clinical Settings

Shulgin and Nichols were the first to report on the effects of MDMA in humans [67]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety [73]. Legal therapeutic use continued until its placement on the U.S. list of Schedule I drugs in 1985 [72, 76, 594]. An estimated 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling [65, 594]. A few uncontrolled human studies of MDMA occurred in the 1980s [51, 70], including Greer and Tolbert's study of MDMA in a psychotherapeutic context.

Controlled human studies of MDMA commenced in the mid-1990s with a MAPS funded investigator-initiated Phase 1 dose-response safety study [54, 595]. MAPS also funded a Phase 2 investigator-initiated dose-response safety and efficacy pilot study in Spain that was terminated early due to political concerns. This study enrolled six participants, with four receiving a single session of MDMA-assisted psychotherapy without any safety concerns and experiencing some PTSD symptom reduction [596].

Based on past reports of MDMA use, nonclinical studies and the results from these investigator-initiated trials with MDMA, the sponsor launched a Phase 2 Clinical Development Program in 2001 to develop MDMA-assisted psychotherapy for the treatment of chronic PTSD under U.S. IND. Nine sponsor-supported Phase 2 studies of MDMA-assisted psychotherapy for PTSD have been conducted. Four have been published - one main study with an extension in three subjects who relapsed in the U.S. (MP-1, MP1-E2) [43, 44], one in Switzerland (MP-2)[45], two US-based studies (MP-8, MP-12) [47, 102], and a pooled analysis of six Phase 2 studies (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12) [101]. One study in Israel was terminated early (MP-3). Two Phase 1 studies (MT-1, MPVA-4), two Phase 2 studies (MP16, MP17) and one Phase 3 study (MAPP1) are ongoing.

MP-1, the first Phase 2 proof of principle study, explored the effect of MDMA-assisted psychotherapy for PTSD with a 125 mg initial dose and 62.5 mg supplemental dose of MDMA, as compared with inactive placebo in a chronic PTSD population (N=23). MP-1 enrolled eighteen women and five men, all European-American, average age 41.3±7.1 years. Participants had no history of major medical conditions, psychotic disorders, dissociative identity disorder, or borderline personality disorder. Safety data obtained included: cognitive function before and after study participation, vital signs, liver panels, psychological distress during experimental sessions, concomitant medications, and AEs. Three MP-1 participants relapsed after treatment, two of them during the 3.8-year follow-up period and one after the follow-up. These three participants were enrolled in an extension study, MP1-E2, to understand if a single MDMA-assisted psychotherapy session would improve PTSD symptoms after a relapse. The study has been completed. One subject experienced an unrelated SAE, a major depressive episode with suicidal ideation. MP-1 and MP1-E2 are now complete.

MP-2, the second Phase 2 proof of principle study, was conducted in Switzerland (N=14). This study explored reproducibility of MDMA-assisted psychotherapy for PTSD with a 125 mg initial dose and 62.5 mg supplemental dose of MDMA, as compared with 25 mg active placebo initial dose and 12.5 mg supplemental dose of MDMA (N=14). MP-2 enrolled 11 women and three men, average age 41.8±10.9 years. Most were of European ethnicity; one woman was South African, and one man was Middle Eastern. Participants enrolled had no psychotic disorders, dissociative identity disorder, or borderline personality disorder. One subject had a previous history of breast cancer that had been in remission for over 10 years and was not symptomatic at screening. Safety data obtained from this study included: vital signs and psychological distress during experimental sessions, liver panels before and after treatment, concomitant medications, and AEs. One subject was diagnosed with a metastatic brain tumor during follow-up that resulted in death, which was an unrelated SAE. A second subject was hospitalized prior to dosing for psychiatric crisis, also reported as an unrelated SAE. MP-2 is now complete.

MP-3, the third Phase 2 study, was conducted in Israel with two Israeli therapist teams. This study was designed to explore reproducibility of MDMA-assisted psychotherapy for endemic PTSD with a 125 mg initial dose and 62.5 mg supplemental dose of MDMA, as compared with 25 mg active placebo initial dose and 12.5 mg supplemental dose of MDMA (N=5). MP-3 enrolled five male participants , average age 39.4±15.9 years, with PTSD symptoms that failed to respond to at least one course of psychotherapy or at least one course of pharmacotherapy. Two participants were Middle Eastern and three were European. This study was terminated early due to personnel turnover at the clinical site and difficulty of ensuring consistent training of site staff. These participants are included in demographics data and excluded from all other data due to inconsistencies in data collection. No SAEs or severe AEs were reported in this study.

MAPS has completed one Phase 1 study and six Phase 2 investigations of MDMA-assisted psychotherapy with one extension study [101]. These studies explored the reproducibility of treatment outcomes of MDMA-assisted psychotherapy in people with chronic PTSD that failed to respond to at least one course of psychotherapy or at least one course of pharmacotherapy. Two of the randomized, blinded studies took place in the U.S. MP-8 (N=26) compared 30 mg versus 75 mg versus 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose, in military veterans, firefighters and police officers ("first responders") with service-related PTSD, with an average age of 37.2±10.3 years. MP-12 (N=28) compared 40 mg versus 100 mg versus 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose, in participants with PTSD from any cause, with an average age of 42.0±12.9 years. The Canadian study MP-4 (N=6) compared placebo to 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose, in participants with an average age of 47.7±6.0 years, and MP-9 (N=10) in Israel compared an initial dose of 25 mg to 125 mg MDMA, with an optional supplemental dose equivalent to half the initial dose, in participants with an average age of 36.7±8.0 years.

The sponsor has completed two additional Phase 2 studies of MDMA-assisted therapies in parallel indications: one for treatment of social anxiety in autistic adults (MAA-1, N=12), and another for anxiety associated with a life-threatening illness (MDA-1, N=18). The Sponsor has completed an open-label study of a combination of MDMA-assisted psychotherapy and cognitive behavioral conjoint therapy in six dyads that include a participant with PTSD and a participant with relationship distress (MPVA-1, N=12).

Two multi-site Phase 2 open-label studies (MP16 and MP17) of MDMA-assisted psychotherapy for PTSD are ongoing. MDMA (80 mg or 120 mg with an optional supplemental dose equal to half of the initial dose) is administered in three psychotherapy sessions, with non-drug

preparatory and integrative sessions. The aim of these studies was to give supervision to newly trained therapy teams prior to participating in the Phase 3 trials.

MPVA-4 is a Phase 1, randomized, placebo-controlled, double-blinded between-groups study in healthy participants examining the effects of MDMA on presence and intensity of startle response after receiving cues that were previous related to a startling stimulus. People will receive 100 mg MDMA or placebo and undergo another startle-related task with the same cues, but without the same stimuli. Subjective effects, mood, and reactions are also being assessed in the ongoing Phase 1 placebo-controlled study of MDMA-assisted psychotherapy, in healthy volunteers who have completed training in manualized MDMA-assisted psychotherapy (MT-1).

MAPP1 and MAPP2 are two Phase 3 studies being conducted as pivotal trials to support an NDA with the FDA. These multi-site trials randomized participants (n=100/trial) in a 1:1 ratio to receive MDMA or inactive placebo during 3 psychotherapy sessions, with 3 integrative sessions following each experimental session. The dosing regimen is 80 mg for the first session, and optional titration dose of 120 mg during the second and third session. An optional supplemental dose equal to half the initial dose is available during the sessions. MAPP1 began enrollment in November 2018.

In sponsor-supported studies, MDMA or placebo/comparator is administered after preparatory psychotherapy during two or three 8-hour experimental sessions scheduled 2 to 5 weeks apart, each followed by at least three sessions of integrative psychotherapy. This treatment model is based on historical experience with MDMA use as an adjunct to psychotherapy.

Most data reported is from the Phase 2 studies of MDMA-assisted psychotherapy for PTSD. The studies have employed a range of comparator and active doses, from an initial dose of 25 mg to 150 mg MDMA. The highest dose (150 mg) was offered to a limited number of participants in MP-2 as part of "Stage 3," an open-label arm for non-responders in Stage 1 and/or Stage 2. All studies have employed 125 mg usually followed 1.5 to 2 hours later by a supplemental dose of 62.5 mg MDMA as the primary active treatment.

The effects in humans presented in the sections below will include findings from both sponsor-supported clinical trials in patient populations as well as studies conducted in controlled laboratory settings in healthy volunteers without sponsor support. Findings from extensive human research being conducted on the pharmacology and mechanism of action will be presented in addition to the information required by FDA in order to support the safety profile of MDMA.

5.2 Pharmacology in Humans

As of May 31, 2019, the sponsor has not conducted studies on the pharmacodynamics or pharmacokinetics of MDMA but relies on published literature. The Sponsor is embarking on conducting pharmacokinetic studies in humans to assess the effects of liver function and effects of food or diet on MDMA metabolism, with the first study planned to start in the fall of 2019. Beginning in the early to mid-1990s, several research teams conducted studies of the pharmacodynamics and pharmacokinetics of MDMA [11, 14, 22, 29, 129, 374, 597-599] without receiving sponsor support. Findings from these teams are described below, with specifics of metabolism detailed in Section 5.2.1 Pharmacokinetics.

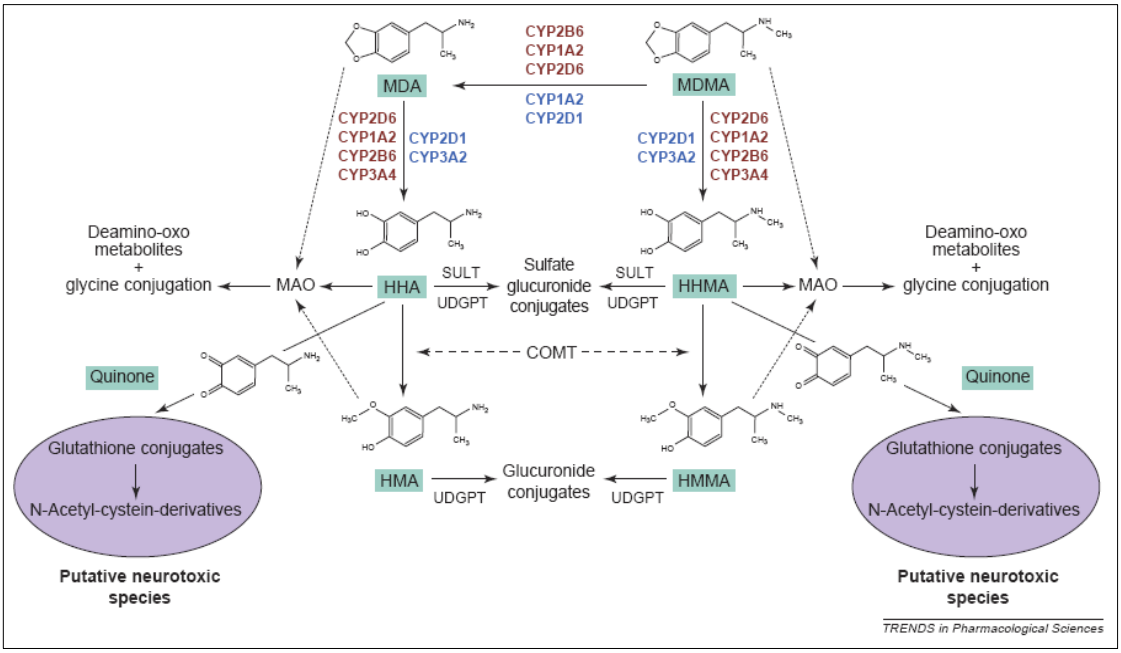
5.2.1 Pharmacokinetics

Onset of MDMA effects occurs 30 to 60 minutes after administration [8, 9], peak effects appear 75 to 120 minutes post-drug [7, 10-12], and duration of effects lasts from 3 to 6 hours [10, 11,

13], with most effects returning to baseline or near-baseline levels 6 hours after final drug administration. Self-reported duration of effects may increase as the dose of MDMA increases [7]. Administering a second dose of MDMA 2 hours after the initial dose, twice that of the initial dose, does not significantly extend the duration of measurable physiological or subjective effects [375]. Orally administered MDMA has a half-life of 7 to 8 hours in humans, with one report listing a half-life of 11 hours [600], and half-life is marginally extended if an additional dose is administered 2 hours after an initial dose [375]. Metabolites of MDMA are summarized in Figure 1 [601-606]. Metabolites are primarily excreted as glucuronide and sulfate conjugates [603, 607, 608], with some evidence for stereoselective metabolism of the glucuronide and sulfate metabolites [607] . Studies examining metabolism of 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates [131, 600, 609-611]. MDMA and its only active metabolite MDA appear in oral fluid samples at much higher concentrations than plasma, for 24 to 48 hours for the former and 12 to 47 hours for the latter after oral administration of 1 to 1.6 mg/kg MDMA [612]. Urinary excretion of the metabolite HHMA after 100 mg MDMA in four men was 91.8±23.8 mol and 17.7% recovery [611]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [613]. As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher when a second dose of 100 mg MDMA was administered 24 hours after an initial dose of 100 mg MDMA when compared with a single dose [131]. In one study, urinary excretion of the metabolite HMMA exceeded that of MDMA by 33 hours after a dose of 1.6 mg/kg MDMA [614], suggesting that secondary metabolism of MDMA continues during this period. Findings support the enantioselective nonlinear metabolism of MDMA, and its metabolites measured in blood and urine [615-617]. CYP2D6 may be involved in stereoselective metabolism of MDMA, but to a clinically insignificant degree [617].

A study comparing the effects of a single 100 mg dose with an initial administration of 50 mg followed 2 hours later by 100 mg reported higher peak plasma MDMA than might be expected, and lower levels of the MDMA metabolites HMMA and HMA [375], findings further supported by examining plasma MDMA after two doses of 100 mg given 4 hours apart [618], likely due to metabolic autoinhibition. Comparison of pharmacokinetic-pharmacodynamic relationships for MDMA reveals acute pharmacodynamic tolerance. Despite 8 hours of plasma half-life of MDMA, and persistent high drug levels in the blood, most pharmacodynamic effects of the initial dose rapidly return to baseline within 4 to 6 hours [599]. These findings suggest that intensity of most subjective and physiological effects of MDMA would not be significantly impacted by the supplemental doses in sponsor-supported studies due to acute tolerance to its prototypical effects [618]. This acute tolerance could be caused by functional depletion of stores of serotonin so that no more can be released despite MDMA still being present [599], or suggests that MDMA transport into intracellular spaces is saturable due to limited transport capacity [141]. Additionally, reversible inhibition of tryptophan hydroxylase as observed in rodents [20], or internalization of serotonin reuptake transporters from the plasma membrane leading to less serotonin release [86], would support self-limiting effects of MDMA. On the other hand, although SERT can be internalized, evidence suggests that accumulation of extracellular serotonin stimulated by MDMA affects SERT trafficking by perpetuating cell-surface SERT expression, but in contrast promotes internalization of DAT and NET [141, 619].

Figure 1: Metabolism of MDMA in Humans



Metabolism of MDMA in humans (in red) compared to metabolism in rats (in blue). Reproduced with permission of R. de la Torre [126].

MDMA is metabolized in the liver by several cytochrome P450 CYP enzymes, including CYP1A2, CYP3A4, and CYP2D6. It is likely that active doses of MDMA inhibit CYP2D6 function, as measured by examining the effects of MDMA on dextromethorphan metabolism. Inhibition of CYP2D6 by MDMA was demonstrated first in a physiological model derived from data collected after oral administration in humans [620]. O'Mathuna and colleagues present evidence that CYP2D6 activity may not fully recover until 10 days after MDMA [621, 622]. After reviewing their data and the literature on MDMA pharmacokinetics, de la Torre and colleagues concluded variation in CYP2D6 genotype is not clinically significant, due in part to the fact that the enzyme is inhibited in most people after administration of an active dose [374]. MDMA may produce increased activity of the enzyme CYP1A2, as evidenced by comparing caffeine metabolism before and after MDMA [623]. The effects of variation in genotypes for the enzymes CYP2C19, CYP2B6 and CYP1A2 on metabolism of 75 and 125 mg MDMA in a pooled sample of 139 participants found that variants with less functional versions of CYP2C19 and CYP2B6 exhibited higher C_{max} for MDMA and increased levels of MDA, and two participants with the poor metabolizer variants of CYP2C19 had greater cardiovascular response to MDMA, and tobacco smokers with inducible CYP1A2 exhibited higher conversion of MDMA to MDA [624]. These results demonstrate compensatory mechanisms that involve contributions from multiple enzymes when CYP2D6 is inhibited through a metabolic complex with MDMA. A pair of in vitro studies modeling metabolism in human liver cells and insect cells reported that CYP2D6 may have functional heterogeneity, or variation in response to substrates, and that less than 50% of CYP2D6 may be inhibited by MDMA, and concluded that the ability of MDMA to inhibit CYP2D6 may be overestimated [625]. The in vitro models seem at odds with lingering reduction in activity detected in humans described above.

The enzyme COMT and monoamine oxidase may also be involved in the metabolism of MDMA [613]. At least one variation in COMT genotype may affect MDMA elimination rate (K_e) and systolic blood pressure (SBP) after MDMA [626]. As a monoamine reuptake inhibitor that leads to monoamine release and inhibits monoamine oxidase-A [146] combining MDMA with a monoamine oxidase inhibitor (MAOI) medication presents a risk for provoking serotonin

syndrome and increases in sympathetic activity. Fatalities have occurred apparently as a result of combining MAOI medications with MDMA [147, 148]. For this reason, MAOI medications are tapered for at least five half-lives of the medication and active metabolites, plus 1 week for symptom stabilization in sponsor-supported studies.

An examination of subjective, physiological and pharmacokinetic effects of variations in genes tied to the serotonin system in a sample of 124 participants sought to investigate differences in plasma levels after 125 mg MDMA[627]. While they detected a slight increase in cumulative MDMA levels (AUC) in one variant of the 5-HT_{1A} receptor and very slight decrease in C_{max} MDMA levels in variant of the $5HT_{1B}$ receptor, neither effect was found to be significant after correcting for number of tests.

Researchers have attempted to compare MDMA pharmacokinetics in humans and other species, including other primates, as also discussed in Section 4.2.1 Pharmacokinetics in Animals. These investigations sought to establish human-equivalent doses given nonlinear pharmacokinetics. Doses that researchers assumed to be human-equivalent produced greater plasma concentrations. However, duration of exposure expressed in half-life was often shorter. For example, a dose of 1.6 mg/kg MDMA produced a half-life of 8.4 hours in a small sample of humans while a dose of 2.8 mg/kg had a half-life of 2.1 hours [132]. A dose of 7.4 mg/kg in squirrel monkeys, four times a human-equivalent dose and never administered in a human trial, had a half-life of 3.4 hours [119]. Researchers have detected nonlinear pharmacokinetics of MDMA in all species studied to date, leading Mueller and colleagues to conclude that a preclinical study cannot accurately and simultaneously model human-equivalent plasma levels and equivalent duration of exposure [132].

5.2.2 Pharmacodynamics

Estimates from animal data suggest the LD50 in humans is probably between 10 to 20 mg/kg [6]. Typically, human trials have used doses between 1 and 2 mg/kg, with therapeutic studies using fixed dosing rather than adjusting dosing on a mg/kg basis, in order to achieve a more consistent subjective response between individuals . The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA [14]. MDMA is a triple monoamine reuptake inhibitor, and similar drugs in this class have been found to exert potent anti-depressant activity with a potentially favorable safety profile [15, 16]. MDMA concomitantly promotes release, inhibits reuptake, and extends duration of serotonin, norepinephrine, and dopamine in the synaptic cleft to increase serotonergic, noradrenergic, and dopaminergic neurotransmission. MDMA has self-limiting subjective and physiological effects as previously described.

Many researchers categorize MDMA as belonging to a unique class of drugs referred to as the Entactogens [13, 74], defined as substances that produce changes in mood and social interaction, as well as feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens [8, 11, 12, 628], as well as a small number of pharmacologically related compounds, such as MDE [628]. Initially, narrative reports and surveys supported the social cognitive effects of MDMA or Ecstasy [2, 266, 267, 629]. Controlled trials detected self-reported empathy or closeness to others in healthy volunteers [7, 10, 99], and starting in the late 2000s to 2010s, controlled studies measured effects of MDMA on social cognition or emotion [29, 30, 37]. Although researchers have offered several models and explanations for the effects of Entactogens, it appears that serotonin and norepinephrine release play a significant role in producing at least some of these effects. Indirect action on $5HT_{1A}$ or $5HT_{2A}$ receptors and neuroendocrine responses such as increases in the hormones oxytocin, AVP, prolactin, and cortisol may also play a role in producing the unique effects of MDMA.

In addition to neuroendocrine and norepinephrine-mediated effects, MDMA may target similar binding sites on the SERT, as do already approved PTSD medications Paxil and Zoloft, which are both SSRIs. Like the SSRI Prozac, MDMA also inhibits MAO-A to extend presence of serotonin in the synaptic cleft [146]. Pre-treatment or co-administration studies of SSRIs with MDMA appear to attenuate or eliminate most subjective, physiological and immunological effects of MDMA due to competition for binding sites on the SERT which may prevent transporter-mediated serotonin release [99, 630-633]. Pre-treatment or co-administration with SSRIs attenuates serotonergic effects of MDMA on mood and perception, without influencing specific effects, such as nervousness or excitability [630]. Some researchers report that SSRIs attenuate MDMA-induced increases in heart rate and blood pressure [99, 631], while others report that SSRIs only attenuate elevated heart rate [633]. Additional effects of each SSRI beyond reuptake inhibition on production, release, and degradation of serotonin are likely responsible for variations between SSRI co-administration findings. All three studies of SSRI pre-treatment suggest that co-administration of SSRIs with MDMA is safe, but the combination prevents or significantly reduces the subjective effects of MDMA.

The role of serotonin release on the potentially therapeutic effects of MDMA-assisted psychotherapy has yet to be investigated, however reduced feelings of sociability and closeness to others after paroxetine pre-administration suggests that serotonin release is at least partially involved in prosocial effects that are thought to be therapeutically relevant [99]. These subjective effects are predominately mediated by direct or indirect action on $5HT_{2A}$ receptors [100, 265, 634], with at least one study concluding that the effects of MDMA upon positive mood are at least due in part to $5HT_{2A}$ receptor activation [100]. In contrast, the $5HT_{1A}$ receptor appears to be partially involved in producing the subjective effects of MDMA [100, 263-265]. Co-administration of the beta-blocker and $5HT_{1A}$ antagonist, pindolol, along with 1.5 mg/kg MDMA to 15 men attenuated self-reported "dreaminess" and pleasantly experienced derealization after MDMA without attenuating MDMA-related reduction in performance on a task requiring visual attention, and co-administration of pindolol failed to alter the acute effects of 75 mg MDMA on self-reported mood [100, 263].

Variations in genes related to serotonin synthesis and three serotonin receptors ($5HT_{1A}$, $5HT_{1B}$, and $5HT_{2A}$), and SERT made very little difference in vital signs or subjective effects of 125 mg MDMA in a study in 124 healthy controls [627]. Gene variants in the $5HT_{2A}$ receptor, SERT and tryptophan hydroxylase-1 influenced subjective effects, a variant in the tryptophan hydroxylase enzyme resulted in higher body temperature after MDMA, and a variation in the $5HT_{1A}$ receptor influenced metabolism. Variants of the tryptophan hydroxylase gene was associated with increased lack of appetite, and one variant of the $5HT_{2A}$ receptor was associate with less reported dizziness after MDMA. However, these effects were no longer significant after correcting for number of tests, likely due in part to a sample size insufficiently powered to perform these tests. Pooled analyses of a sample of 132 healthy participants who received 125 mg MDMA in placebo-controlled studies reported that variation in an oxytocin receptor gene (rs1042778TT) reported greater feelings of trust after MDMA, but that variations in oxytocin receptor genes did not affect cognitive or emotional empathy [35].

Human MDMA studies suggest that norepinephrine release also contributes to the pharmacodynamic, physiological and psychological effects of MDMA [229, 232, 635, 636]. Tricyclic antidepressants, as well as many of the current antidepressant medications, are known to promote norepinephrine signaling, as does MDMA. Studies with the norepinephrine uptake inhibitor reboxetine, and the α_1-adrenergic receptor antagonist doxazosin, suggest that norepinephrine plays a role in the effects of MDMA on blood pressure and subjective effects of positive mood and excitement [230, 635], but not in "entactogenic" or "empathogenic" effects.

Most of the psychostimulant-like and psychological effects of MDMA are blocked after administration of the dual selective serotonin and norepinephrine uptake inhibitor (SNRI) duloxetine [232, 636]. There is evidence that norepinephrine and serotonin may play a role in the elevation in the neuroendocrine hormone copeptin, the C-terminal precursor of pre-pro-AVP, detected in women acutely after MDMA administration [636]. Some *in vitro* findings with human monoamine transporters expressed in cells indicate that MDMA displays a higher affinity for the NET than the serotonin or dopamine transporter, while still producing greater detectable release of serotonin versus norepinephrine, suggesting a role for both transmitter systems [141]. As the NET unexpectedly has a greater affinity than the DAT for dopamine, it preferentially clears dopamine in brain areas where there is a greater concentration of NET, such as the frontal cortex [637]. The relative affinities of MDMA for various monoamine reuptake transporters, and the affinity of the respective transporters for each neurotransmitter, can thus influence the selectivity of signaling pathways MDMA activates in a region-specific manner depending on transporter density and availability.

Some MDMA effects on human mood and anxiety may be attributed to dopamine release based on the finding that pretreatment with haloperidol, a dopamine receptor antagonist with partial selectivity for the D_2 receptor subtype, diminished MDMA-induced positive mood and increased anxiety [638]. However, the control group receiving haloperidol alone also experienced dysphoric mood, suggesting that this finding may overestimate the dopaminergic effects of MDMA. Studies comparing MDMA with the dopaminergic and adrenergic drug methylphenidate (Ritalin) suggest that dopamine release and inhibition of uptake play a minor role, if any, in producing the effects of MDMA [36]. Co-administration of MDMA with the potent dopamine reuptake inhibitor methylphenidate neither enhanced nor attenuated the effects of MDMA [599]. MDMA, but not methylphenidate, increased trust, openness, and closeness to others. Co-administration of MDMA with the dopamine reuptake inhibitor bupropion prolonged, but did not reduce subjective effects of MDMA, supporting that dopamine does not have a part in MDMA effects on mood [639].

MDMA produces a robust increase in the neurohormone oxytocin [29, 31, 640, 641], a finding first seen in a naturalistic study that reported elevated levels of oxytocin in clubgoers with detectable blood MDMA levels when compared to clubgoers without detectable levels of MDMA [32], and confirmed in blinded, placebo-controlled experiments. Preliminary evidence from a study in men given 100 mg MDMA supports a relationship between $5HT_{1A}$ receptor activation and elevated plasma oxytocin [642]. It is likely that all neuroendocrine changes are part of a signaling cascade downstream of monoamine release. Exogenous oxytocin increases trust and improves accuracy of emotion perception, and increased cortisol, in some circumstances, may serve as a signal to seek affiliation or to increase positive mood [643-646]. However, studies comparing increases in empathy or prosocial effects of MDMA with intranasal oxytocin have failed to find indications that the two substances produce similar effects, with MDMA producing greater feelings of sociability and emotional empathy than oxytocin [34, 71]. Peripheral oxytocin has been suggested to be a reliable indicator of central oxytocin, but peripheral effects of oxytocin need to be ruled out when assessing central effects [647]. The potential significance of elevated oxytocin in producing changes in social cognition are discussed in Section 5.3.8.3 Social Effects, and include potentially therapeutic effects, such as increased feelings of closeness to others or greater ability to detect expressions of positive mood in others.

MDMA acutely increases cortisol, prolactin, and adrenocorticotropic hormone concentrations in a dose dependent manner [9, 10, 19, 30, 54, 131, 231, 648-651], whereas growth hormone levels are unchanged by up to 125 mg MDMA [9]. Increases in cortisol and prolactin peak at about 2 hours after MDMA administration [9, 54]. A second dose of 100 mg MDMA, given 4 hours after an initial 100 mg, produces a second increase in cortisol during an interval when cortisol levels are declining [652], and a dose of 100 mg MDMA, given 24 hours after an initial dose, stimulates a greater release of cortisol but not prolactin [131].

In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA, with peak levels appearing 2 to 3 hours post-drug [10]. A crossover study comparing the effects of MDMA and methylphenidate found that MDMA increased serum cortisol while methylphenidate did not, and that neither drug altered testosterone levels [651]. These findings suggest a relationship between serotonin release and increased serum cortisol. Pre-treatment with the cortisol synthesis inhibitor metyrapone blocked MDMA-induced increase in cortisol levels in blood without preventing impaired performance on verbal memory tasks or altering the effects of MDMA on mood [650]. A study investigating the emotional effects of MDMA found no correlation between those changes and the MDMA-induced increases in oxytocin, cortisol, and prolactin [231].

A study applying a high-throughput detection method using liquid chromatography/mass spectrometry to assess changes in chemical markers (the "metabolome"), compared blood before and after 100 mg MDMA in 16 healthy volunteers, and detected elevation in cortisol, pregnenolone and calcitriol, a metabolite of vitamin D after MDMA [648]. Cortisol and pregnenolone were increased 4 hours after MDMA, treated as signs of stress and serotonergic activity. Calcitriol is involved in regulating other compounds that protect dopamine neurons. Boxler and colleagues detected a comparable increase of several factors (hydroxyeicosatetraenoic acid, dihydroxyeicosatetraenoic acid, and octadecadienoic acid) associated with mediating inflammation, and that the authors interpreted as signs of an inflammatory process. If baseline values after MDMA and placebo were the same, the authors used baseline corrections, but did not correct for number of tests, and over 10,000 compounds were detected. The findings appear at odds with immunological findings, wherein 100 mg MDMA was associated in an increase in immunosuppressive and anti-inflammatory cytokines.

The pharmacological basis for reported acute shifts in memory, including impaired visual recall and improved recall for life events, after MDMA administration remains undetermined. Initial findings suggest a relationship between MDMA and activation of temporal areas in the brain and response to positive memories, as well as increases in medial PFC and response to negative memories [39]. It is possible that elevation in cortisol could be tied to specific acute effects on mood or memory. Another study found MDMA-associated changes in inferior parietal lobule and acute impairment in working memory [653]. Animal studies have postulated a role of Ach release triggered by upstream serotonin and dopamine neurons in MDMA-induced shifts in memory described above.

A study applying receptor-enriched mapping and functional connectivity in a sample of 20 men reported that 100 mg MDMA activated brain areas assumed to have high $5HT_{1A}$ density or high levels of SERT density. Despite failing to find a significant change in functional connectivity after MDMA in brain regions high in $5HT_{2A}$ receptors, Dipasquale and colleagues reported that activity seen in these areas after MDMA were associated with reporting a spiritual experience [642]. This investigation also found relationship between time course of MDMA effects and changes in functional connectivity in brain areas associated with $5HT_{1A}$ receptor density. The

report found decreased functional connectivity in several cortical areas, including specific areas of the temporal and frontal cortex, and insula. This research design uses templates that assume receptor distribution, with models related to PET imaging data; the model does not use individual maps of receptor density. No significant association between $5HT_{1B}$ or $5HT_4$ receptor presence and MDMA effects on brain activity.

An investigation of functional connectivity after administering 100 mg to healthy volunteers reported decreased network connectivity in the right insula/salience network [654], with decreased connectivity associated with changes in subjective ratings of trait anxiety and bodily sensations. Since increased insular activity is reported in social anxiety and PTSD, the authors suggest that reduced insular connectivity may be associated with MDMA's therapeutic effects.

A human study revealed no difference in MDMA-induced memory changes following pretreatment with the cortisol synthesis inhibitor metyrapone or the α_7-nAChR receptor antagonist memantine, suggesting cortisol is not involved in these effects [650, 655]. It is unclear what contributions, if any, elevated neuroendocrine levels make to the subjective and memory effects of MDMA.

5.2.3 Neurobiological, Behavioral and Subjective Effects

5.2.3.1 Neurobiological Effects

Early investigations of MDMA in healthy volunteers with PET detected decreased left amygdalar activity and increased frontal activity [28]. PET brain scans 75 minutes after administration of 1.7 mg/kg MDMA found increased regional cerebral blood flow (rCBF) in ventromedial prefrontal, inferior temporal, and cerebellar areas and decreased rCBF in the left amygdala [28]. In a different study, arterial spin labeling has also found decreased cerebral blood flow (CBF) in the right amygdala and hippocampus after MDMA administration [27]. The decreased CBF correlated with drug intensity ratings after 100 mg MDMA. Blood oxygen level dependent (BOLD) MRI scans of resting-state functional connectivity in the same sample detected complementary decreases in medial PFC-hippocampal coupling and increases in right amygdala-hippocampal coupling, although the relationship did not achieve statistical significance [27]. Decreased activity in the amygdala may be indicative of reduced reactions to potential threats [656]. MDMA (100 mg) increased subjective ratings of positive mood in response to positive memories and decreased negative response to negative memories. Attenuated activity in the left anterior temporal area was detected after MDMA during worst memory recall [39].

During a task that required keeping a visual target cue in mind, visual attention, and response inhibition, brain imaging detected changes in parietal activity after 75 mg MDMA compared with placebo [653]. MDMA increased activity in frontal areas and decreased activity in occipital sites as measured via functional MRI (fMRI) [657]. Reduced resting-state cerebral blood flow in right amygdala and hippocampus after MDMA was associated with greater intensity of self-reported subjective effects [27]. Participants given MDMA exhibited similar brain activity when reading or encoding a word list, suggesting that they were investing similar effort into both tasks. Ten ecstasy users receiving a minimum of two doses of 1-1.25 mg/kg or 2.25-2.5 mg/kg MDMA exhibited signal decreases in bilateral visual cortex, caudate, superior parietal, and dorsolateral frontal regions 10 to 21 days later, with increased rCBF measured in two participants at a later time point [658]. However, a comparison between heavy Ecstasy users and non-user controls failed to find differences in baseline rCBF [28], and a report assessing changes before and after initial Ecstasy use found increased rCBF in only one area of the prefrontal cortex [307], suggesting that the changes seen by Chang and colleagues are a transient effect. EEG recorded 2 hours after MDMA administration showed the following changes in EEG activity: overall

increase in beta activity, reduction in alpha activity, localized decreases in alpha and delta in frontal areas, and increased frontotemporal beta signal [659]. The authors reported the EEG patterns after MDMA were similar to those seen with serotonergic and noradrenergic drugs, as well as, but to a lesser extent, dopaminergic drugs.

5.2.3.2 Behavioral and Neuropsychological Effects

Perception and Cognition

Research has assessed perception and cognition acutely after MDMA, commonly at doses between 75 and 125 mg (or 0.5 go 1.5 mg/kg). In studies of healthy controls, MDMA causes slight changes in visual or auditory perception, including changes in the brightness or colors, sounds seeming closer or farther away, and simple visual distortions [7, 8, 10, 11]. Study participants experienced altered time perception, and changes in meaning or significance of perceptions after MDMA [13].

One early study in a pooled, largely drug-naïve sample reported gender differences in intensity of subjective effects, with women reporting greater intensity of all subjective effects, and especially perceptual effects [11]. A second study pooling data across three separate samples and including people with and without prior experience with "Ecstasy or MDMA," did not find any significant gender effects (Kirkpatrick 2014-Basel-Chicago-SF).

The perceptual effects of MDMA appear to be the result of direct or indirect action on $5HT_{2A}$ receptors, as co-administration of the $5HT_{2A}$ antagonist ketanserin reduced reported perceptual alterations, as well as eliminated slight elevations in body temperature after 1.5 mg/kg MDMA [634], while co-administration with the $5HT_{1A}$ antagonist pindolol did not affect perceptual alteration [263]. The effects of MDMA upon perception have not been studied within sponsor-supported studies. Uncorrected findings from a study of variations in serotonin-related genes across a pooled sample reported that people with a variant of the $5HT_{2A}$ gene reported experiencing more "good drug effect," "trust" and "high mood," and "dreaminess," and people with a variant in the $5HT_{1A}$ gene reported higher "good drug effect," "closeness to others", and lower ratings of "bad drug effect" [627]. People with a variant of the SERT gene reported greater "fear" and 'depression" after MDMA. These associations support the role of serotonin as a major contributor to producing the subjective effects of MDMA, but they were also no longer significant after correcting for number of tests. The study was likely underpowered for genetic analyses of four genes in a sample not selected for this purpose. For more details on the acute effects of MDMA on perception and cognition, see Sections 5.3.8.1 and 5.3.8.2

Affect and Emotion

MDMA increases positive mood and anxiety [8, 10-12] on measures of alteration in consciousness and subjective effects. There is evidence that increases in positive mood and anxiety increase with dose [8, 10, 37, 251]. MDMA users report feeling more talkative and friendly after receiving MDMA. Self-reported interpersonal closeness was noted during a study in healthy volunteers [13, 29, 30]. Subsequent research confirmed the occurrence of increased interpersonal closeness after MDMA [37, 99, 633]. Researchers using two items within an instrument designed to assess drug effects and a visual analog scale rating closeness to others failed to detect increased feelings of empathy after 1.5 mg/kg MDMA [10], possibly due to the low sensitivity of these measures.

In another investigation, the SSRI paroxetine was pre-administered to healthy volunteers before administering MDMA. The researchers found that MDMA increased feelings of being social and

closeness to others, and paroxetine reduced these effects, indicating a significant role of the serotonergic system for the prosocial effects of MDMA [99]. People have reported feeling anxious or experiencing negative derealization while under the influence of MDMA, including increased anxiety related to loss of control and experiences of racing or blocked thoughts [8, 11, 13]. More information on the effects of MDMA on affect may be found in section 5.3,8.4.

An examination of personality assessed prior to and after receiving MDMA-assisted psychotherapy from a sponsor-supported study (MP-1) reported increased openness to experience and decreased neuroticism after MDMA when compared with placebo [660], a finding similar to findings reported in studies of people given the classic psychedelic psilocybin [661, 662]. Wagner and colleagues also found that changes in openness, but not neuroticism, were associated with reductions in PTSD symptoms [660].

Social Effects

In controlled laboratory settings, an established measure of accurate facial expression reading found that MDMA improved detection of expressions of positive mood and reduced accuracy in detecting expressions of negative mood [30]. Despite initial findings in naturalistic studies suggesting that Ecstasy increased accuracy of assessing some emotional expressions, particularly fearful ones [663], an fMRI study found that 0.75 and 1.5 mg/kg MDMA reduced signaling in the amygdala in response to angry faces when compared with placebo without changing the response to faces showing fear [26]. These researchers also detected increased activity in the ventral striatum in response to happy faces. Taken together, these findings suggest that MDMA changes the way emotional facial expressions are processed or the response to them. There is increased interest in the social effects of MDMA and proposals to use it as a tool for better understanding human social cognition and interaction [664].

Complementing these findings are results demonstrating that MDMA enhanced the accuracy of recognizing facial expressions of positive mood and impaired mind reading for facial expressions of negative mood but had no effect on mind reading for neutral faces [30]. Enhanced mind reading of positive emotions may facilitate therapeutic relationships in MDMA-assisted psychotherapeutic settings. In addition, and contrary to the finding in the early naturalistic study described above, there is some evidence showing that MDMA produces selective difficulty in recognizing faces expressing fear [665]. Further investigation corroborates this finding, showing that MDMA reduced recognition accuracy of fear significantly more in women than in men, and reduced recognition accuracy of sadness in women, but not in men. The same study found MDMA-induced increases in both implicit and explicit emotional empathy in men, but not in women [19].

At least four research teams published relevant findings in studies of healthy volunteers during 2013 and 2014, examining the effects of MDMA on social cognition with several experimental paradigms assessing brain activity during episodic memory recall and contributions of oxytocin and cortisol to the acute effects of MDMA. Findings include reduced reactivity to simulated social exclusion, reduced negative emotional response to self-selected "worst" memories, increased use of language related to interpersonal closeness, increased emotional empathy and increased perceived partner empathy. One study reported greater social language after MDMA than with the psychostimulant methamphetamine [40], and another reported greater emotional empathy after MDMA and another psychostimulant, methylphenidate [36]. An examination assessing the impact of variation in serotonin-related genes upon the effects of MDMA in a pooled sample of 124 participants reported decreased cognitive empathy and increased emotional empathy for positive emotions without reporting any variation due to genotype [627]. Taken together, this research lends greater support to the view that MDMA possesses unique

psychological effects, distinct from psychostimulants that can be beneficial when combined with psychotherapy. As an entactogen, MDMA can promote increased trust, greater ability to face and cope with emotionally distressing memories, thoughts or feelings and greater emotional empathy toward oneself and others.

Findings in placebo-controlled trials suggest that MDMA enhances positive response to positive social stimuli. Wardle and colleagues observe this effect simultaneously with a decrease in positive response to positive stimuli with no social content, which suggests that the contrast in valuation of social and non-social emotional stimuli contributes to MDMA's prosocial effects [41]. MDMA also reduces the impact of rejection on mood and self-esteem [666], which manifests more strikingly at lower doses of MDMA than reduction in perceived social rejection, suggesting complex social and behavioral effects from MDMA.

Moreover, results from Kirkpatrick and colleagues show a behavioral preference for social activities over non-social ones, with subjects reporting increased desire for only the social activity after 1.5 mg/kg MDMA [667]. One study reported increased generosity in monetary allocation to a friend after 1.5 mg/kg MDMA compared with placebo and increased generosity toward a stranger in women after 0.5 mg/kg MDMA [668], while a study examining the effects of 125 mg MDMA on empathy and resource allocation reported that MDMA increased prosocial behavior in men [19]. Men playing a "Prisoner's Dilemma" were more likely to cooperate with a trustworthy opponent (an opponent who did not defect often) after receiving 100 mg MDMA than after receiving placebo, without increasing cooperation with an untrustworthy opponent [38]. Findings ran counter to expectations that MDMA would foster higher ratings of trustworthiness overall and cooperating with both types of opponent. Neuroimaging of participants' brain activity suggests that MDMA altered activity in the left temporal lobe and insula, and increased activity in the dorsal caudate when interacting with the trustworthy opponent. The authors hypothesized that increased cooperation after MDMA was driven not by increased ratings of trustworthiness, but of reduced likelihood of defecting, and of being upset or angry, at occasional defection in the trustworthy opponent, and possibly in increased reward value, assumed from increased dorsal caudate activity.

In a study by Bedi and colleagues, MDMA induced changes in semantic speech content measured with natural language learning software. Through natural language processing (NLP), researchers found speech patterns after MDMA were distinct from those produced after methamphetamine and placebo [40]. Proximity of speech to the concepts of *friend*, *support*, *intimacy*, *rapport*, and *empathy* was increased in the MDMA drug condition, which may bear some significance for the use of MDMA in therapy. MDMA did not affect the overall structure of participants' speech. These findings were confirmed in an additional sample through a standardized dictionary method and machine learning, indicating that MDMA increased the use of social words, as well as words connoting positive and negative emotions [280]. There is some evidence that the increases in affiliative and prosocial feelings are separable from romantic or sexual feelings. Men and women did not seek to prolong viewing of images with explicit sexual content after MDMA, and they did not impute increased romantic feelings to images of heterosexual couples [669]. A systematic examination of statements (discourse) from participants enrolled in MAPS' study MP-1 conducted by an independent researcher found greater attention to and concern for the therapists and others in participants receiving MDMA versus inactive placebo [670].

While the hormone oxytocin is implicated in social interactions and bonding, evidence indicates that oxytocin alone does not explain MDMA's prosocial effects. One investigation found a positive correlation in subjective effects ratings between intranasal oxytocin and oral MDMA, but only at the lower of the two oxytocin doses tested [71]. Using pindolol to block 5-HT_{1A} receptor mediation of oxytocin's effects, Kuypers and colleagues determined that MDMA increased

emotional empathy while oxytocin did not produce similar effects on measures of empathy and social interaction [34]. A subsequent report from the same researchers pooling data across six placebo-controlled within-subjects' studies in 118 participants confirmed an increase in emotional empathy without an increase in cognitive empathy [641], noting a specific increase in emotional empathy for positive emotions. MDMA administration but were not associated with subjective effects between subjects. According to Kuypers, oxytocin did not affect measures of empathy and social interaction, and changes in emotional empathy were not related to oxytocin plasma levels [34]. However, interpretation is limited because Kuypers and colleagues [34, 641]did not measure within-subject correlation of subjective effects with multiple post-MDMA oxytocin levels as in study design that showed a positive within-subject correlation after MDMA for oxytocin and prosocial effects [29].

Studies examining the prosocial effects of MDMA, in relation to oxytocin, should be considered in the context of previous findings that showed no discernable subjective effects were found for intranasal oxytocin [671]. A single nucleotide polymorphism in the oxytocin receptor gene was found to predict subjective responses to MDMA, suggesting that this question remains worthy of further study [672]. Two studies have found that MDMA increased AVP [291, 636]. Neither study reported analysis or findings concerning any relationship between AVP levels and the subjective, emotional or social effects of MDMA.

Studies in healthy controls comparing doses between 0.75 and 1 mg/kg and 1.5 to 2 mg/kg suggest that the higher dose produces greater prosocial effects than the lower dose, while the lower dose may increase self-reported loneliness and use of empathy-related language [41, 42, 666, 673]. It is notable that one study found a gender-specific trend for greater generosity after a lower (0.5 mg/kg) dose than a higher one [668]. However, higher doses also produce a greater degree of stimulation and anxiety. It is notable that the first study investigating the impact of variation in an oxytocin receptor gene reported that those with one variation did not exhibit an increase in sociability after 1.5 mg/kg without a statistically significant difference in response at 0.75 mg/kg [672].

When combined with psychotherapy, MDMA permits people to confront and consider emotionally intense memories, thoughts, or feelings, and perhaps through changes in mood and perception, increase empathy and compassion for others and oneself [43, 70, 596]. In a sub-study of MP-8, the Self Compassion Scale [674] was administered before and 2 months after MDMA-assisted psychotherapy. Preliminary results in this small sub-study (N=7) were trending upward; participants were low in self-compassion with mean total score of 2.4±0.63 prior to the study and experienced an increase to moderate self-compassion with mean total score of 2.8±0.84. In this assessment, self-kindness and a sense of common humanity increased, while self-judgment and feelings of isolation decreased on average within-subjects.

A Phase 1 study of the effects of MDMA-assisted psychotherapy on mood and social cognition in healthy volunteers who completed training in performing manualized MDMA-assisted psychotherapy is underway. Findings will include effect on mood and interpersonal closeness. The MAA-1 study in autistic adults measured symptoms of social anxiety, with secondary measures of emotion identification in the self and others, emotion regulation, alexithymia, and empathy. In this study, biomarkers associated with social behavior, including oxytocin, AVP, and cortisol, were assessed before, during, and after MDMA-assisted therapy. Findings from ongoing studies will assist the sponsor in evaluating how neuropsychological effects contribute to mechanism of action of MDMA-assisted psychotherapy.

5.3 Safety of MDMA in Humans

Safety data from studies in controlled research settings show that MDMA produces sympathomimetic effects that include statistically significant, self-limiting increases in body temperature, heart rate, and blood pressure that are likely to be transient and well tolerated by healthy individuals [7, 9-11, 26, 43-45, 51-54, 595, 596, 675]. Risks posed by elevated blood pressure are addressed in clinical trials by excluding candidates with a history of cardiovascular or cerebrovascular disease or with pre-existing uncontrolled hypertension and by monitoring blood pressure and pulse during MDMA-assisted experimental sessions. Common reactions from MDMA research studies are transient and diminish as drug effects wane during treatment sessions and over the next 24 hours. In studies conducted with and without sponsor support in controlled clinical settings, with 1837 individuals exposed to MDMA, there have been no published or reported unexpected SARs to date, and expected SARs have been rare and non-life threatening. One subject to date experienced an expected SAR (increased ventricular extrasystoles in MP-8) reported in MAPS-sponsored clinical trials.

All sponsor-supported non-serious safety data (adverse events, spontaneously reported reactions, vitals during experimental sessions, and suicidal ideation and behavior) are presented in this IB through a cutoff date of 01 October 2018 unless indicated otherwise.

There are eight completed Phase 2 studies (MP-1, MP1-E2, MP-2, MP-4, MP-8, MP-9, MP-12, MPVA-1) and two ongoing Phase 2 studies (MP16, MP17) of MDMA-assisted psychotherapy in people with PTSD, and a completed open-label Phase 1/Phase 2 study in a dyad that includes a participant with and a participant without PTSD (MPVA-1). A Phase 2 study of MDMA-assisted therapy treating social anxiety in autistic adults (MAA-1) and another Phase 2 study of MDMA-assisted psychotherapy treating anxiety associated with life-threatening illness (MDA-1) have been completed. Safety is addressed and closely monitored through several measures in these studies. Vital signs, concomitant medications, unexpected and expected AEs are collected in all studies. Suicidal ideation and behavior are formally measured with the Columbia Suicide Severity Rating Scale (C-SSRS) in all but MP-1 and MP-2. Three completed studies (MP-1, MP-12, MP-4) measured cognitive function before and after treatment. Psychological distress during psychotherapy sessions is assessed in most Phase 2 studies with the single-item Subjective Units of Distress (SUD) scale.

Partial safety data from the Phase 1 study MT-1 in healthy volunteers is not presented in the current report since data remains blinded. There have been no severe or serious AEs during the study, and there were no clinically significant changes in vital signs. No medical intervention has been required for AEs during this study to date.

Physiological effects of MDMA-assisted psychotherapy in sponsored studies are similar to those reported in studies conducted outside of sponsor support, including elevated blood pressure, body temperature, and heart rate. The following common reactions are found in published literature and are collected in the sponsor's Phase 2 clinical trials: anxiety, depressed mood, insomnia, obsessive rumination, restlessness, irritability, headache, disturbance in attention, dizziness, paresthesia, impaired judgment, hypersomnia, nausea, diarrhea, fatigue, asthenia, feeling cold, muscle tightness, decreased appetite, hyperhidrosis, disturbed gait, dry mouth, thirst, sensation of heaviness, somnolence, and nystagmus.

These common reactions are transient and diminish as the drug is metabolized during treatment sessions and excreted over the next 24 hours, with the majority of reactions resolving within several days and up to 1 week after dosing. Among spontaneous reports of reactions to MDMA, muscle tightness (jaw), anxiety, decreased appetite, headache, and fatigue were most commonly

reported acutely during MDMA-assisted psychotherapy. During the week following treatment, the most frequently reported reactions were anxiety, fatigue, insomnia, depressed mood, and hypersomnia. The half-life of MDMA doses used in these studies is 8 to 9 hours and the majority of AEs have been transient, resolving within 2 to 3 days after MDMA has been metabolized and excreted. Severe anxiety, insomnia, fatigue, nausea, muscle tightness, and depressed mood are commonly reported in PTSD studies supported by the sponsor. These reactions also overlap with symptoms of pre-existing conditions in medical history associated with PTSD (depression, somatic symptoms, insomnia, anxiety), which may influence the reaction frequency observed during clinical trials of MDMA-assisted psychotherapy.

5.3.1 Reproductive and Developmental

All research studies with MDMA, with and without sponsor support, require measures to limit pregnancy risk prior to receiving each dose of MDMA. People of childbearing potential must use an effective method of birth control to be enrolled in sponsor-supported studies, and pregnancy tests must be negative prior to each experimental session. There is no information on reproductive and developmental risks reported since there have been no pregnancies in these studies. See Section 4.4.5 Reproductive and Developmental Toxicity for information gathered on reproductive and developmental risks in Ecstasy users.

5.3.2 Immunological Effects

Various groups have studied immunological effects of MDMA in laboratory settings, with none found to be clinically significant from a safety standpoint. Studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects [130, 632, 652, 676, 677]. Findings included a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and INF-γ, and increased production of anti-inflammatory cytokines, including IL-10 and TGF-ß. Generally, MDMA appeared to decrease the concentration of Th1 cytokines, including IL-2, and increase the amount of Th2 cytokines, including IL-4, measured in blood. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [130, 677]. Due to their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. Interestingly, meta-analysis and meta-regression of 20 studies investigating inflammatory markers in PTSD found an association with increased IL-6, IL-1β, TNF-α, and INF-γ, consistent with chronic low-grade inflammation [206], and any effects of MDMA on these immune markers remains to be tested.

Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given 4 hours after the first dose [652, 678]. A second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose [652]. Given this data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose will slightly enhance the immunological effects set in motion by the initial dose of MDMA. Previous Phase 1 studies mentioned above have not reported any indication of increased risk of illness occurring after MDMA administration.

5.3.3 Thermoregulatory Effects

In the first Phase 1 safety study funded by the sponsor, MDMA was found to cause a significant increase in body temperature in some healthy volunteers [54]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Doses between 1.5 and 2 mg/kg produced only a slight elevation in body temperature that was not clinically significant [11, 631, 634, 675] and this elevation was unaffected by ambient temperature [219]. Studies in MDMA-experienced volunteers given 2 mg/kg MDMA produced slight but statistically significant increases in core body temperature, at mean elevation of 0.6°C [219]. The same study found that ambient temperatures did not affect elevation in core temperature after administration of MDMA, which increased metabolic rate. A supplemental dose twice as large as the initial dose of MDMA elevates body temperature, but not beyond what would be expected after the cumulative dose [375]. While MDMA did not increase or decrease perspiration overall in this study, it was associated with a higher core temperature when perspiration began.

Ambient temperature neither attenuated nor amplified the subjective effects of MDMA, with people reporting similar drug effects in warm and cool environments. As expected, people felt warm when the room was warm and cold when the ambient temperature was cool, and MDMA did not distort perceptions of warmth or cold in either case. Unlike rodents given MDMA at higher mg/kg doses, humans do not exhibit reduced temperature when MDMA is given in a cold environment, and they do not exhibit significant hyperthermia in a warm environment.

When compared with placebo, findings from 74 people that were given MDMA found that men exhibited a greater elevation in body temperature than women when given the dose of MDMA in mg/kg [11]. Subsequent studies have not confirmed this gender difference [26], and a report in a sample of 17 men and women reported higher oral temperatures in women [626]. Prior to correction for number of tests, a study on the effects of serotonin-related genotypes on MDMA reported higher body temperature in people with a variant of the TPH-2 gene, but these findings were no longer significant after applying corrections [627]. A review of clinical placebo-controlled laboratory studies conducted without sponsor support found that route of measurement influences variability in body temperature findings, with oral and tympanic, but not axillary, temperatures frequently rising above 38°C into moderate hyperthermia ranges at 125 mg MDMA. Thermogenic effects of MDMA are distinct from malignant hyperthermia and are mediated by noradrenergic signaling, which contributes to peripheral effects of MDMA by affecting cutaneous vasoconstriction of blood flow and stimulation of heat production, and are attenuated by norepinephrine blocking drugs . It is notable that participants in studies in a clinical setting have not engaged in vigorous exercise and have remained either sitting or lying down throughout duration of drug effects. It may be the case that heat dissipation impaired by a hot environment, heat generation increased by exertion, interactions of serotonergic drugs, and potential disturbance of central heat regulation mechanisms contribute to the occurrence of hyperpyrexia (body temperatures >41°C) in people ingesting Ecstasy in uncontrolled settings. However, one of four naturalistic studies reported that Ecstasy users had a statistically significant increase in body temperature [679], while three others failed to find significant differences in Ecstasy-user body temperature at a club [680-682].

In most sponsor-supported studies to date, tympanic body temperature readings were taken at baseline, then every 60 to 90 minutes, with some differences in collection methods across studies. Peak values during each experimental session are ascertainable for all studies. Across studies, the final value was either at a relatively set time (MP-8, MP-12, MP1-E2, MP16, MP17, MPVA-1) or as the final reading with time point varying (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and these were averaged. Average post-drug values serve as the final value for MP-2. If body temperature rose 1°C above the pre-drug

reading, each duration above specific values requiring more frequent assessment listed in study protocols, from 160/110 mm hg (MP-1, MP-4, MP-9, MP-12, MPVA-1, MP-8) to 180/120 mm Hg (MAA-1, MDA-1) Clinical signs and symptoms were monitored, and more frequent readings were collected in cases where readings were above these values. .

Body temperature data presented below is final for completed studies and preliminary for studies ongoing at the time of data cutoff. The data is presented grouped by indication: PTSD studies in aggregate and independently due to changes is data collection (MP16, MP17); Social Anxiety study (MAA-1); and Anxiety associated with Life Threatening illness (MDA-1).

Table 3: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with BT 1 ° C above Baseline
0 mg	10	36.4 (0.51) 35.1/37.2	36.9 (0.36) 36.4/37.6	36.6 (0.36) 35.9/37.5	2 (20.0)
25 mg	8	36.4 (0.39) 35.5/37.1	37.2 (0.78) 36.0/38.5	36.8 (0.65) 35.4/38.0	4 (50.0)
30 mg	7	36.2 (0.47) 35.3/36.9	37.0 (0.42) 36.4/37.9	36.6 (0.47) 35.7/37.3	4 (57.1)
40 mg	6	36.4 (0.50) 35.8/37.2	37.1 (0.33) 36.6/37.6	37.0 (0.38) 36.5/37.6	2 (33.3)
75 mg	7	36.6 (0.46) 35.9/37.8	37.1 (0.52) 36.3/37.8	36.7 (0.42) 36.1/37.3	2 (28.6)
100 mg	9	35.9 (1.00) 33.9/37.9	37.0 (0.64) 35.5/38.7	36.5 (0.74) 34.8/38.1	4 (44.4)
125 mg	58	36.5 (0.47) 35.4/37.6	37.3 (0.49) 36.1/38.6	36.9 (0.54) 34.5/38.2	26 (44.8)
Open-label (100-150 mg)	78	36.4 (0.54) 34.3/37.7	37.3 (0.57) 36.0/38.7	36.8 (0.58) 35.2/38.4	39 (50.0)

Body temperature was assessed periodically every 60 to 90 minutes throughout each experimental session. All studies recorded pre-drug and post-drug or average post-drug body temperature, and peak temperature was either recorded directly or was selected from among all recorded values. In MAPS-sponsored PTSD studies, body temperature above (1°C above pre-drug reading) was detected in 44% (42 of 95) participants who received MDMA at any dose during blinded sessions and 50% (39 of 78) participants receiving 100-150 mg MDMA during open-label sessions. Note that body temperature above 1°C above pre-drug reading was observed in 20% (2 of 10) of participants who received placebo. End of session temperature readings were lower than peak drug readings, though they remained above pre-drug measurements. Body temperature increases that were 1°C or more above initial temperature occurred in all dose groups, suggesting a minimal role for dose. The maximum body temperature observed for any subject receiving MDMA was 38.7°C, observed after a 100 mg blinded session and during open-label sessions. No participants required medical intervention to decrease body temperature, and values returned to baseline as drug effects waned. There was no need for medical intervention in addressing elevated body temperature. Body temperature measured during experimental sessions in Sponsor-supported studies of PTSD is commensurate with values seen in Phase 1 clinical trials described above.

Table 4: Pre-Drug, Midpoint, and Final Body Temperature (ºC) During Open-label MDMA Sessions in MAPS-Sponsored Studies of PTSD (MP16 and MP17) as of October 1, 2018

Dose	N[a]	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
Open-label (80-120 mg)	28	36.7 (0.40) 35.5/37.5	37.1 (0.51) 35.9/38.7	36.9 (0.42) 35.9/37.6

[a] MDMA session 1 (n=28), MDMA session 3 (n=25)

In MP16 and MP17, vitals were assessed on the day of MDMA sessions prior to drug dosing, just before the optional supplemental dose (midpoint), and at the end of the session. The maximum body temperature observed for any subject receiving MDMA was 38.7°C, and the mean (SD) temperature prior to the supplemental dose was 37.1°C.

Table 5: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with 1 ° C above Pre-Drug
0 mg	4	36.5 (0.23) 36.1/36.8	36.8 (0.12) 36.6/36.9	36.7 (0.20) 36.4/36.9	0
75 mg	4	36.6 (0.45) 36.2/37.2	37.2 (0.29) 36.9/37.6	37.0 (0.19) 36.7/37.2	0
100 mg	7	36.6 (0.50) 35.9/37.3	37.3 (0.33) 36.7/37.7	37.2 (0.31) 36.6/37.6	2 (28.6)
125 mg	4	37.1 (0.23) 36.8/37.4	37.4 (0.26) 37.2/37.7	37.3 (0.08) 37.2/37.4	0
Open-label (75 mg)	4	36.7 (0.26) 36.4/36.9	37.2 (0.35) 36.7/37.6	37.1 (0.35) 36.7/37.6	0
Open-label (125 mg)	4	36.6 (0.19) 36.4/36.9	37.2 (0.26) 36.8/37.4	36.9 (0.36) 36.4/37.2	0

In the MAPS study MAA-1, body temperature 1°C above pre-drug reading was detected in 28.6% (2 of 7) participants who received 100 mg during a blinded session. Body temperature above the 1 ° C increased pre-determined for increased assessment did not occur during open-label sessions with 75 or 125 mg MDMA. The maximum body temperature observed for any subject receiving MDMA was 37.7°C. No participants required medical intervention to decrease body temperature, and values dropped below peak values or returned to baseline as drug effects waned. Body temperature measurements in this sample are similar to those reported in Phase 1 studies and the sample of people with PTSD.

Table 6: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Placebo or Full MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with BT 1 ° C above Pre-Drug
0 mg	5	36.4 (0.43) 35.7/36.9	36.9 (0.27) 36.5/37.5	36.4 (0.56) 35.0/37.0	1 (20.0)

125 mg	13	36.3 (0.49) 35.6/37.4	37.3 (0.71) 36.1/39.9	36.9 (0.44) 35.9/37.6	7 (53.8)
Open-label (125 mg)	17	36.3 (0.44) 35.4/37.2	37.3 (0.33) 36.6/38.0	36.9 (0.39) 36.0/37.4	9 (52.9)

In the MAPS study MDA-1, body temperature rose 1°C above pre-drug reading in 53.8% (7 of 13) of participants receiving MDMA during blinded experimental sessions and in none of the participants given placebo during blinded sessions. Body temperature rose 1 ° C above pre-drug reading in 52.9% (9 of 17) participants during open-label sessions. Body temperature recorded at end of session was lower than peak body temperature. The maximum body temperature observed for any subject receiving MDMA was 39.9°C, observed with 125 mg MDMA. No participants required medical intervention to decrease body temperature, and values returned to baseline as drug effects waned.

Table 7: Pre-Drug, Peak, and Final Body Temperature (ºC) During Experimental Sessions with Full MDMA Dose in MAPS-Sponsored MPVA-1 Study

Group/Dose	N	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
PTSD+ Open-label (75-100 mg)	6	36.8 (0.44) 36.2/37.7	37.2 (0.48) 36.5/38.4	37.1 (0.40) 36.5/37.6
CSO Open-label (75-100 mg)	6	36.5 (0.29) 36.0/37.3	37.1 (0.53) 36.4/38.1	37.0 (0.63) 35.8/38.0

In MPVA-1, vitals were assessed on the day of MDMA sessions prior to drug dosing, just before the optional supplemental dose (midpoint), and at the end of the session. The maximum body temperature observed for any subject receiving MDMA was 38.4°C, and the mean (SD) temperature prior to the supplemental dose was 37.1°C (CSO) and 37.2°C (PTSD+).

Based on the literature, MDMA is expected to produce elevations in body temperature with possible influence of ambient temperature. In the above MAPS-sponsored studies, adjustments were made to the ambient temperature and to air circulation in the room in response to observed elevation in body temperatures, but no participants required medical intervention to decrease body temperature, and values returned to baseline as drug effects waned. In conclusion, controlled setting for treatments with MDMA-assisted psychotherapy are optimized with the capacity to control ambient temperature for subject comfort, though there is no evidence that this will significantly influence or is needed for control of core body temperature.

5.3.4 Cardiovascular Effects

MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing [51] and replicated by other research teams in the U.S. and Europe [9, 11, 52, 675]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [7, 10, 26, 53]. Most people do not experience elevations that are greater than those seen after moderate exercise. MDMA has also been found to decrease respiratory sinus arrhythmia, the natural variation in heart rate over the course of each respiratory cycle [683]. Cardiovascular effects of MDMA first appear 30 to 45 minutes after administration [51] and peak between 1- and 2-hours post-drug [12, 52], with effects waning 3 to 5 hours after drug administration. Men given the same mg/kg dose of MDMA as women exhibited a significantly greater elevation in blood pressure and heart rate in a study summarizing and pooling data from a series of human MDMA studies [11]. These studies did not report any discomfort or increased distress accompanying cardiovascular effects.

Elevation in blood pressure above 140/90 mmHg occurred in approximately 5% of research participants receiving a single dose of at least 100 mg of MDMA in Phase 1 research studies [9, 13]. Peiro and colleagues observed elevation in blood pressure above 150/90 as well in all 10 participants given 50 mg followed 2 hours later by 100 mg MDMA [375]. When compared with 100 mg MDMA and placebo given 4 hours apart, two doses of 100 mg 4 hours apart significantly elevated SBP, while other physiological were not significantly elevated beyond values seen after a single dose. These studies used different dosing regimens than the one used in sponsor-supported studies, which employ an optional supplemental half dose. None of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [9, 13, 375].

Greater elevations in blood pressure are seen in individuals with a specific COMT genotype (Val158Met genotype), and greater elevations in blood pressure and heart rate are seen in individuals with a specific SERT (l/* 5-HTTLPR) genotype [626]. However, the observed increases are not so severe as to suggest contraindication for these genotypes. The α_1- and beta-adrenergic receptor antagonist carvedilol is capable of reducing MDMA-induced elevations in blood pressure, heart rate, and body temperature when administered 1 hour before MDMA without affecting the subjective effects of MDMA, indicating the norepinephrine release is primarily responsible for cardiovascular effects of MDMA [231]. Other concomitant antihypertensive medications either alter some of the effects of MDMA [665] or do not significantly reduce MDMA-induced blood pressure elevation [229].

Norepinephrine release induced by MDMA leads to indirect activation of the AVP system, stimulating secretion of copeptin (CTproAVP), a 39-aminoacid glycopeptide that is a C-terminal part of the precursor pre-proAVP. CTproAVP is secreted into circulation from the posterior pituitary gland in equimolar amounts with AVP. CTproAVP directly reflects AVP concentration and can be used as a surrogate biomarker of AVP secretion. In many studies CTproAVP behavior represents changes in plasma osmolality, stress and various disease states (diabetes, SIADH, heart failure, renal disorders), and is an indicator of osmoregulatory function in the body [418]. Heart failure is commonly associated with hyponatremia, and is also characterized by increased concentrations of basal AVP and CTproAVP [428]. Intra-cardiac pressures, intra-arterial pressures, angiotensin II, pain, and adrenergic (α_2) central nervous stimuli can also influence AVP secretion [417]. Increased CTproAVP concentration is described in several studies as a strong predictor of mortality in patients with chronic heart failure and acute heart failure. [418]. Taken together, the AVP system appears to be the main connection between MDMA and cardiovascular risk as well as hyponatremia.

In all sponsor-supported studies to date, blood pressure readings were taken at baseline, with study-specific differences in data collection times post-drug. Peak values during each experimental session are ascertainable for all studies, except MP16, MP17, and MPVA-1 where vitals were collected just prior to the optional supplemental dose (midpoint in tables below). The final or endpoint was recorded as the final value, either at a relatively set time (MP-8, MP-12, MP16, MP17, MPVA-1) or as the final value available, or with timepoint varying (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and these were averaged, whereas all other studies reported single time point pre-drug. Average post-drug values serve as the final value for MP-2. If systolic blood pressure (SBP) rose above 160 mmHg or if diastolic blood pressure (DBP) rose above 110 mmHg, each duration above this pre-determined cut-off for more frequent measurement was collected in MP-8, MP-12, MP-9, and MP-4. In MAA-1, if SBP rose above 180 mmHg or if DBP rose above 110 mmHg, each duration above the pre-determined cut-off was collected. If SBP rose above 180 mmHg and if DBP rose above 120 mmHg, each duration above the pre-determined cut-off is collected in MDA-1. MP-2 criteria for cut-off was exceeding both 160/110 mmHg. Clinical signs and symptoms were monitored, and more frequent readings were collected in cases where readings were above cut-off.

Systolic Blood Pressure

SBP data presented below is final for completed studies and preliminary for studies ongoing at the time of data cutoff. The data is separated by indication into tables (PTSD studies in aggregate; Social Anxiety in People on the Autism Spectrum study/MAA-1; and Anxiety associated with Life Threatening Illness/MDA-1). Values recorded during blinded sessions are separately reported from values collected during open-label sessions.

Table 8: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with SBP Above 160 mm Hg
0 mg	10	114.9 (11.61) 90.5/136.5	129.7 (15.27) 102.0/157.0	111.4 (12.88) 83.0/133.0	0
25 mg	8	119.3 (7.13) 107.0/141.0	132.5 (9.09) 114.0/147.0	119.3 (11.23) 107.0/146.0	0
30 mg	7	114.0 (11.91) 94.0/134.0	132.3 (14.02) 110.0/155.0	118.5 (11.63) 98.0/140.0	0
40 mg	6	124.7 (14.14) 100.0/154.0	134.3 (15.47) 112.0/163.0	123.6 (12.52) 107.0/148.0	1 (16.7)
75 mg	7	125.4 (9.99) 109.0/145.0	147.0 (14.43) 123.0/179.0	127.4 (11.85) 107.0/147.0	1 (14.3)
100 mg	9	121.4 (20.16) 96.0/161.0	138.6 (23.55) 100.0/180.0	116.7 (13.50) 92.0/140.0	2 (22.2)
125 mg	58	126.2 (16.03) 98.0/177.0	153.7 (18.49) 114.0/200.0	127.3 (16.25) 86.0/168.0	26 (44.8)
Open-label 100-150 mg	78	124.1 (14.37) 95.0/171.0	151.1 (17.10) 105.0/193.0	124.7 (14.88) 77.0/161.0	28 (35.9)

The rise in SBP was greater in doses of 75 mg or more. In MAPS-sponsored PTSD studies, systolic blood pressure above 160 mmHg was detected in 32% (30 of 95) participants who received MDMA at any dose during blinded sessions. It is notable that the majority of these cases occurred after 125 mg but failed to occur after inactive placebo or doses lower than 30 mg. SBP rose above 160 mm Hg in 36% (28 of 78) participants after 100 to 150 mg in open-label sessions. As is the case for blinded sessions, SBP returned to baseline levels at the end of the session. The maximum systolic blood pressure for any subject receiving MDMA was 200 mmHg. Final (end of session) values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Table 9: Pre-Drug, Midpoint, and Final Systolic Blood Pressure During Open-label MDMA Sessions in MAPS-Sponsored MP16 and MP17 Studies of PTSD as of October 1, 2018

Dose	N[a]	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
Open-label 80-120 mg	28	126.1 (14.80) 97.0/172.0	145.3 (14.14) 110.0/181.0	124.7 (12.39) 92.0/158.0

[a] The number of participants was n=28 at experimental session 1, and n=25 at experimental session 3.

Across three open-label sessions, participants with PTSD experienced an increase in SBP values post-drug at the midpoint, taken prior to the optional supplemental dose. SBP returned to pre-drug levels by the final reading. The max recorded SBP was 181 mmHg.

Table 10: Pre-Drug, Midpoint, and Final Systolic Blood Pressure During Open-label MDMA Sessions in MAPS-Sponsored for MPVA-1 Study

Group/Dose	N	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
PTSD+	6	121.1 (16.18)	133.9 (16.23)	123.7 (9.80)
Open-label 75-100 mg		100.0/160.0	113.0/175.0	109.0/139.0
CSO	6	121.7 (16.81)	138.5 (21.82)	122.2 (19.88)
Open-label 75-100 mg		100.0/160.0	97.0/180.0	97.0/162.0

After two open-label sessions with 75-100 mg MDMA, both members of dyads consisting of people with PTSD and concerned significant others exhibited a rise in systolic blood pressure in a study of MDMA-assisted psychotherapy and cognitive-behavioral conjoint therapy (CBCT). SBP returned to near baseline levels at the closing of an experimental session, with final readings 0.5 to 2.6 units higher than baseline. Additional or high SBP values were not recorded for any of the participants. Peak SBP was not recorded. Observed SBP did not appear to differ on the basis of PTSD diagnosis. Maximum recorded SBP during this study was 180 mmHg in a concerned significant other at experimental session midpoint.

Table 11: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with SBP Above 180 mm Hg
0 mg	4	131.0 (11.6) 112.0/144.0	142.5 (11.8) 126.0/159.0	126.9 (5.6) 121.0/138.0	0
75 mg	4	117.5 (14.8) 101.0/137.0	136.3 (26.3) 116.0/174.0	122.0 (10.7) 112.0/134.0	0
100 mg	7	113.3 (12.9) 92.0/133.0	121.4 (9.4) 113.0/141.0	114.6 (10.2) 105.0/135.0	0
125 mg	4	114.8 (5.1) 109.0/120.0	123.5 (14.6) 110.0/143.0	114.0 (4.1) 111.0/120.0	0
Open-label 75 mg	4	124 (11.0) 116.0/140.0	138.8 (17.0) 127.0/164.0	131.8 (17.6) 114.0/156.0	0
Open-label 125 mg	4	131.0 (3.9) 126.0/135.0	153.0 (17.6) 135.0/170.0	142.8 (19.1) 127.0/170.0	0

In the MAA-1 study, systolic blood pressure did not rise above 180 mmHg)during blinded sessions with inactive placebo or 75-125 mg MDMA, nor during open-label sessions with 75-125 mg MDMA. The maximum systolic blood pressure for any subject receiving MDMA was 174 mmHg, occurring after 75 mg MDMA. Observing peak SBP values in this sample suggests slightly lower values than in studies in people with PTSD, but the sample is much smaller, and this may reflect a chance fluctuation. It is also notable that in general, this study employed lower active doses than the PTSD studies. Final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Table 12: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or Full MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with SBP Above 180 mm Hg
0 mg	5	127.5 (13.34) 102.0/145.0	146.0 (15.53) 126.0/173.0	119.7 (8.71) 106.0/135.0	2 (40.0)
125 mg	13	129.9 (17.94) 91.0/178.0	157.54 (17.05) 127.0/192.0	125.69 (11.45) 103.0/145.0	7 (53.8)
Open-label 125 mg	17	129.1 (19.13) 78.0/162.0	157.0 (18.64) 119.0/196.0	128.0 (13.8) 106.0/153.0	5 (29.4)

In the MDA-1 study, systolic blood pressure rose above threshold (180 mmHg) in 54% (7 of 13) of participants who received 125 mg MDMA during blinded sessions and in 29% (5 of 17) after open-label 125 mg sessions. In comparison, SBP above 180 mm Hg was detected in 40 % (2 of 5) of participants who received placebo. The maximum systolic blood pressure for any subject receiving MDMA was 196 mmHg, observed after 125 mg in an open-label session. Final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure. SBP values in this sample appear to be similar to values reported in sample with PTSD.

As described above, MDMA is expected to produce statistically significant but transient, self-limited increases in blood pressure. The supplemental half dose, when administered 1.5 to 2.5 hours after the initial dose, may cause further SBP increases above that of the initial dose of MDMA. In one study (MP-1), 9 of 23 participants received the supplemental dose, with four in the 125 mg MDMA group. In all subsequent studies, most of the participants received the optional supplemental dose. A comparison of participants receiving the supplemental dose to those who only received the initial dose in MP-1 indicated that the supplemental dose did not cause further elevation in blood pressure and heart rate beyond the initial dose, although the sample was underpowered to detect a small effect. Maximum SBP observed to date was 200 mmHg in a single MP-2 subject, lasting 5 hours, where 125 mg MDMA was administered as the initial dose. This subject had a medical history of controlled hypertension, and the traumatic event that caused PTSD was medical malpractice, with a secondary diagnosis of white coat hypertension. This subject was only enrolled after 24-hour monitoring of blood pressure at baseline to confirm this diagnosis. Despite elevations in SBP, no clinical signs or symptoms of hypertension were observed.

Candidates with hypertension were excluded from participation in early sponsor-supported studies, but more recent studies have allowed enrollment of participants with well controlled hypertension. For example, in MP-8 four participants with hypertension controlled by medications were permitted to enroll after completion of carotid ultrasound and nuclear stress test (per protocol) in addition to usual medical screening for the study. SBP results are depicted below.

Table 13: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions in Controlled Hypertension Participants in MAPS-Sponsored PTSD Study MP-8

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	SBP Above 160 mm HG N
30 mg	1	125 125/125	131 131/131	124 124/124	0
75 mg	1	139 (8.49) 133/145	174.5 (6.36) 170/179	147 147/147	1
125 mg	2	130.8 (11.53) 124/148	160.5 (13.30) 147/177	128.5 (9.54) 118/141	2
Open-label 100-125 mg	3	139.2 (18.97) 122/171	174.6 (18.47) 144/193	142.8 (10.28) 133/158	2

Systolic blood pressure above 160 mmHg was detected in 75% (3 of 4) of participants with controlled hypertension during blinded sessions with 30-125 mg MDMA and in 67% (2 of 3) participants receiving 100-125 mg MDMA during open-label sessions. This did not occur after administration of 30 mg MDMA. The maximum systolic blood pressure for these participants with controlled hypertension was 193 mmHg, occurring during an open-label session. The baseline values and elevations after MDMA appear higher in this sub-group than the overall sample, although the means could decrease in a larger group. Pre-drug SBP was typically higher in this sub-group, and peak SBP of these participants was typically at the upper end of the range of the overall sample. Final SBP readings remained 11 to 14 mmHg higher on average than pre-drug SBP readings in the subject who received 75 mg of MDMA in two blinded experimental sessions and 100 mg in three open-label crossover experimental sessions. However, two participants receiving 125 mg MDMA had final readings that returned to pre-drug values, suggesting this could be an individual case with a medical history of both hypertension and hyperlipidemia. One subject with controlled hypertension dropped out (not due to blood pressure concerns) after receiving a single experimental session with 30 mg MDMA but did not experience SBP above 160 None of the participants with controlled hypertension experienced AEs of the cardiovascular system, and SBP returned to baseline or near-baseline at final session reading.

In all cases across studies, final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Diastolic Blood Pressure

Diastolic blood pressure (DBP) data presented below is final for completed studies and preliminary for studies ongoing at the time of data cutoff. The data is separated by indication into tables (PTSD studies in aggregate; Social Anxiety in People on the Autism Spectrum study/MAA-1; and Anxiety associated with Life Threatening illness/MDA-1). Each table is divided by dose within blinded experimental sessions and open-label sessions.

Table 14: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with DBP Above 110 mm Hg
0 mg	10	72.7 (7.88) 56.5/87.5	83.4 (9.73) 65.0/102.0	68.5 (9.71) 48.0/89.0	0
25 mg	8	73.4 (6.44) 59.0/84.0	82.7 (5.30) 74.0/92.0	71.9 (5.43) 63.0/81.0	0
30 mg	7	73.5 (8.03) 60.0/87.0	85.5 (7.52) 75.0/99.0	76.7 (6.23) 68.0/91.0	0
40 mg	6	80.0 (9.96) 62.0/95.0	86.1 (9.28) 72.0/96.0	79.9 (9.74) 68.0/96.0	0
75 mg	7	77.9 (9.73) 56.0/95.0	91.4 (12.06) 78.0/118.0	78.4 (11.19) 59.0/100.0	1 (14.3)
100 mg	9	79.0 (13.45) 58.0/102.0	84.4 (11.38) 65.0/101.0	74.4 (7.72) 61.0/88.0	0
125 mg	58	79.5 (10.03) 52.0/102.0	92.5 (10.88) 70.0/135.0	78.6 (10.27) 53.0/104.0	6 (10.3)
Open-label 100-150 mg	78	78.1 (9.31) 56.0/103.0	92.8 (10.8) 64.0/126.0	77.5 (9.79) 54.0/100.0	5 (6.4)

In MAPS-sponsored PTSD studies, doses of 75 and 125 mg MDMA produced greater elevation in DBP than lower doses, such as 25 to 40 mg. This was not always the case, as observed with peak DBP after 100 mg MDMA, but the lesser increase in DBP may reflect random variation in a small sample. At the end of session or final reading, DBP had returned to baseline levels across all doses of MDMA. DBP above 110 mmHg was detected in 7% (7 of 95) of participants who received any dose of MDMA during blinded study sessions, and 6.4% (5 of 78) participants who received 100-150 mg MDMA during open-label sessions. The maximum diastolic blood pressure for any subject receiving MDMA was 135 mmHg, and no clinical intervention was required. No clinically significant AEs were reported based on elevations in blood pressure. These observations suggest that people with PTSD experience similar elevations in SBP and DBP as those seen in healthy controls.

Table 15: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Full Dose MDMA in MAPS-Sponsored MPVA-1 Study

Group/Dose	N	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
PTSD+ Open-label 75-100 mg	6	76.3 (8.49) 62.0/91.0	79.9 (8.73) 63.0/94.0	75.4 (8.55) 61.0/87.0
CSO Open-label 75-100 mg	6	72.5 (14.40) 46.0/94.0	83.8 (12.85) 61.0/106.0	76.3 (12.72) 53.0/95.0

In the MAPS-sponsored open-label study of MDMA-assisted psychotherapy and CBCT in dyads made up of one person with PTSD and a significant other without it, DBP was elevated at midpoint compared with baseline in both groups (3.6 to 11.3 units mmHG) and returned to near-baseline after 75-100 mg MDMA. DBP returned to baseline or near baseline at the session's end (dropping 4.5 to 7.5 units). The highest value was recorded at midpoint (106 mm Hg). No additional readings were required during either experimental session.

Table 16: Pre-Drug, Midpoint, and Final Diastolic Blood Pressure During Open-label MDMA Sessions in MAPS-Sponsored MP16 and MP17 Studies of PTSD as of October 1, 2018

Dose	N	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
Open-label 80-120 mg	28	80.4 (10.79) 55.0/107.0	89.4 (10.79) 66.0/119.0	78.1 (10.09) 44.0/103.0

In open-label sessions, DBP rose by 9 mmHg at the midpoint before returning to near baseline levels by session end. The max recorded DBP was 119 mmHg. No additional readings were required during either experimental session.

Table 17: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with DBP Above 110 mm Hg
0 mg	4	76.9 (10.0) 64.0/89.0	82.3 (11.2) 72.0/106.0	74.5 (8.6) 62.0/88.0	0
75 mg	4	68.5 (9.3) 61.0/81.0	80.3 (5.3) 73.0/85.0	68.8 (4.6) 64.0/74.0	0
100 mg	7	60.7 (6.3) 52.0/72.0	76.9 (8.4) 62.0/89.0	67.1 (8.5) 59.0/82.0	0
125 mg	4	67.8 (2.2) 66.0/71.0	78.3 (9.0) 69.0/86.0	68.5 (3.4) 64.0/72.0	0
Open-label 75 mg	4	71.0 (10.8) 62.0/85.0	82.5 (4.7) 77.0/88.0	72.0 (3.5) 69.0/75.0	0
Open-label 125 mg	4	81.5 (8.3) 70.0/88.0	88.3 (7.6) 79.0/95.0	73.0 (7.6) 62.0/78.0	0

In the MAPS-sponsored MAA-1 study, MDMA produced greater elevation in DBP than inactive placebo (rise of 5.4 mmHg after placebo versus a rise of 11.8 mmHg after 75 mg, 15.4 mmHg after 100 mg, and 10.5 mmHg after 125 mg). At end of session, DBP returned to baseline levels in blinded and open-label experimental sessions. DBP above 110 mmHg was not detected during any sessions, regardless of dose. The maximum DBP for any subject receiving MDMA was 106, which occurred after inactive placebo administration. Final (end of session) values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Table 18: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with DBP Above 120 mm Hg
0 mg	5	78.5 (16.49) 4.06/94.0	91.6 (13.40) 72/112	78.4 (11.40) 64/100	1 (20.0)
125 mg	13	78.7 (11.05) 55.0/106.0	93.9 (19.11) 75.0/154.0	73.1 (7.47) 58.0/84.0	4 (30.8)
Open-label 125 mg	17	81.1 (16.09) 50.0/117.0	94.6 (11.69) 72.0/118.0	77.5 (12.66) 52.0/97.0	2 (11.8)

In the MDA-1 study, peak DBP was greater after 125 mg MDMA than after inactive placebo as expected, and final values returned to pre-drug levels with no clinical intervention required. Diastolic blood pressure above 120 mmHg was detected in 31% (4 of 13) participants who received 125 mg MDMA during blinded sessions, and 11.8% (2 of 17) participants receiving MDMA during open-label sessions. In comparison, diastolic blood pressure above threshold was detected in 20% (1 of 5) of participants who received placebo. The maximum diastolic blood pressure for any subject receiving MDMA was 154, observed in a subject who received 125 mg MDMA. No clinically significant AEs were reported based on elevations in blood pressure.

Candidates with hypertension are excluded from participation in early sponsor-supported studies, but now participants with well controlled hypertension can enroll if they satisfy additional screening procedures to rule out significant cardiovascular or cerebrovascular disease. For example, in MP-8 four participants with hypertension controlled by medications were permitted to enroll after completion of carotid ultrasound and nuclear exercise test (per protocol) in addition to usual medical screening for the study. Diastolic blood pressure results are depicted below.

Table 19: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions in Controlled Hypertension Participants in MAPS-Sponsored PTSD Study MP-8

Dose	N (Observations)	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	DBP Above 110 mm Hg N (Observations)
30 mg	1	85 85/85	86 86/86	77 77/77	0
75 mg	1 (2)	92 (4.24) 89/95	115.5 (3.54) 113/118	95.5 (6.36) 91/100	1 (2)
125 mg	2 (4)	86.0 (6.68) 79/95	97.0 (6.06) 91/105	83.0 (7.62) 72/89	0
Open-label 100-125 mg	3 (5)	86.8 (9.39) 77/101	114.4 (13.3) 93/125	91.2 (6.10) 82/99	1 (3)

People with controlled hypertension responded similarly to MDMA as normotensive people, with final values returning to at or near baseline levels, and peak levels higher after 75-125 mg compared with 30 mg MDMA. Diastolic blood pressure above 110 mmHg was detected in 25% (1 of 4) participants with controlled hypertension in blinded sessions and in one of three participants who received 100-125 mg during open-label sessions. The maximum diastolic blood pressure for these participants with controlled hypertension was 125 mmHg. Final values returned to pre-drug levels at end of session with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

In all cases across studies in people with PTSD, autistic adults with social anxiety, and people with anxiety arising from facing a life-threatening illness, blood pressure returned to pre-drug levels at end of session with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Heart Rate

In all sponsor-supported studies to date, heart rate readings were taken at baseline, with study-specific differences in data collection times post-drug. Peak values during each experimental session were ascertainable for all studies. The final or endpoint value was recorded as the final value, either at a relatively set time (MP-4, MP-8, MP-9, MP-12, MP16, MP17, MPVA-1) or as

the final value available, with time point varying (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and these were averaged, whereas all other studies reported single time point pre-drug value. Average post-drug values serve as the final value for MP-2. If heart rate rose above 110 bpm, each duration above the pre-determined cut-off was collected in MP-8, MP-12, MP-9, MP-4. Duration of pulse above cut-off was not collected in MP-2. Clinical signs and symptoms were monitored, and more frequent readings were collected in cases where readings were above cut-off.

Heart rate data presented below is final for completed studies and preliminary for studies ongoing at the time of data cutoff. The data is separated by indication into tables (PTSD studies aggregated; Social Anxiety in People on the Autism Spectrum study/MAA-1; and Anxiety associated with Life Threatening illness/MDA-1).

Table 20: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies of PTSD (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12)

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with HR Above 110 BPM
0 mg	10	64.9 (11.53) 45.0/91.0	77.8 (13.02) 54.0/107.0	67.6 (11.14) 45.0/89.0	0
25 mg	8	69.6 (13.14) 47.0/94.0	84.2 (19.27) 50.0/124.0	72.4 (12.37) 51.0/90.0	2 (25.0)
30 mg	7	67.7 (13.89) 45.0/91.0	81.1 (15.98) 54.0/102.0	72.7 (13.01) 50.0/89.0	0
40 mg	6	79.1 (11.00) 66.0/103.0	87.5 (11.51) 69.0/103.0	80.1 (15.50) 56.0/103.0	0
75 mg	7	73.7 (8.31) 61.0/85.0	96.2 (16.12) 75.0/123.0	82.9 (13.34) 63.0/102.0	2 (28.6)
100 mg	9	70.8 (17.40) 46.0/118.0	97.0 (21.50) 65.0/140.0	81.4 (13.21) 63.0/114.0	3 (33.3)
125 mg	58	74.8 (13.89) 45.0/122.0	103.2 (16.75) 67.0/160.0	85.6 (15.56) 47.0/135.0	29 (50.0)
Open-label 100-150 mg	78	74.0 (14.98) 36.0/116.0	106.0 (20.28) 63.0/156.0	83.7 (14.72) 52.0/120.0	36 (46.2)

In MAPS-sponsored PTSD studies, MDMA appears to increase peak heart rate compared with placebo, with a greater difference between pre-drug and peak values observed with active doses, and nearly greater differences between peak and pre-drug for every dose except for 40 mg during blinded sessions. In PTSD studies, heart rate elevated above 110 bpm was detected in 38% (36 of 95) of participants receiving MDMA in blinded experimental sessions, and heart rate never arose above threshold in inactive placebo. Heart rate was elevated above 110 BPM in 46% (36 of 78) of participants given 100-150 mg MDMA in open-label sessions. The maximum heart rate for any subject receiving MDMA was 160 bpm. Values at end of session returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in heart rate.

Table 21: Pre-Drug, Midpoint, and Final Heart Rate During Open-label MDMA Sessions in MAPS-Sponsored MP16 and MP17 Studies as of October 1, 2018

Dose	N	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
Open-label 80-120 mg	28	70.1 (9.89) 53.0/102.0	93.2 (21.62) 62.0/150.0	82.6 (17.03) 38.0/137.0

During open-label sessions, heart rate rose by 23.1 beats per minute (BPM) at the time of collection prior to the supplemental dose. The max heart rate recorded was 150 BPM. Heart rate was elevated by 12.5 units on average at the session end compared to pre-drug values.

Table 22: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Full Dose MDMA in MAPS-Sponsored MPVA-1 Study

Group/Dose	N	Pre-drug Mean (SD) Min/Max	Midpoint Mean (SD) Min/Max	Final Mean (SD) Min/Max
PTSD+ Open-label 75-100 mg	6	69.3 (12.59) 53.0/93.0	85.1 (23.65) 61.0/137.0	90.8 (19.53) 66.0/131.0
CSO Open-label 75-100 mg	6	72.6 (8.82) 58.0/87.0	94.2 (17.57) 61.0/119.0	87.9 (8.36) 76.0/101.0

In the MAPS-sponsored open-label study of CBCT combined with MDMA-assisted psychotherapy in dyads comprised of a person diagnosed with PTSD and significant other without the diagnosis, heart rate was elevated by 15.8 to 19.6 BPM compared with baseline in participants with and without PTSD, In the MAPS-sponsored open-label study of CBCT combined with MDMA-assisted psychotherapy in dyads comprised of a person diagnosed with PTSD and significant other without the diagnosis, heart rate was recorded at baseline, midpoint and at experimental session end. Mid-session HR was elevated compared with baseline in participants with and without PTSD. Heart rate remained above baseline at the end of the session. The highest value was 137 BPM, recorded at session midpoint in a PTSD participant. No extra readings were taken for any participant.

Table 23: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MAA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with HR Above 110 BPM
0 mg	4	57.3 (9.7) 47.0/78.0	75.3 (10.3) 63.0/94.0	67.4 (7.4) 59.0/83.0	0
75 mg	4	68.0 (3.7) 63.0/72.0	87.0 (14.0) 75.0/105.0	73.8 (6.3) 65.0/80.0	0
100 mg	7	70.0 (12.2) 53.0/88.0	89.3 (12.1) 71.0/105.0	79.1 (15.9) 58.0/100.0	0
125 mg	4	78.5 (12.1) 61.0/88.0	95.0 (19.8) 75.0/114.0	89.3 (13.2) 75.0/101.0	1 (25.0)
Open-label 75 mg	4	58.0 (6.1) 52.0/65.0	71.8 (10.1) 58.0/82.0	66.5 (7.1) 57.0/74.0	0
Open-label 125 mg	4	64.0 (6.9) 58.0/74.0	87.0 (8.1) 80.0/94.0	70.0 (6.2) 63.0/78.0	0

In the MAPS-sponsored MAA-1 study, peak heart rate increases ranged from 15 bpm after inactive placebo to 16.5 bpm after 125 mg MDMA in blinded sessions and ranged from 13-23 bpm after open-label sessions. In most cases, heart rate had returned to baseline levels or near baseline levels, except after blinded 125 mg, where average final reading remained 15.7 bpm greater than baseline. However, this dose group consisted of only three individuals. Heart rate above 110 bpm was detected in 14% (1 of 4) participants given MDMA during blinded experimental sessions and in none of the participants receiving placebo during blinded experimental sessions or after open-label sessions with 75-125 mg MDMA. The maximum heart rate for any subject receiving MDMA was 114 bpm. No clinical intervention was required during the study. No clinically significant AEs were reported based on elevations in heart rate.

Table 24: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored MDA-1 Study

Dose	N	Pre-drug Mean (SD) Min/Max	Peak Mean (SD) Min/Max	Final Mean (SD) Min/Max	N (%) with HR Above 120 BPM
0 mg	5	69.0 (13.88) 50.0/100.0	81.5 (12.26) 71.0/108.0	71.4 (7.11) 60.0/86.0	0
125 mg	13	69.3 (10.74) 53.0/95.0	105.5 (14.44) 89.0/133.0	92.9 (16.43) 69.0/133.0	6 (46.2)
Open-label 125 mg	17	70.3 (10.23) 57.0/91.0	106.8 (17.34) 77.0/140.0	87.1 (13.97) 62.0/117.0	6 (35.3)

In MAPS-sponsored MDA-1, MDMA produced a greater increase in heart rate than inactive placebo during blinded and open-label sessions. End of session heart rate was lower than peak value for all dose groups, with end of session heart rate at pre-drug levels after placebo and lower than peak value but at least 15.5 bpm higher than pre-drug levels after 125 mg MDMA in blinded or open-label sessions. Elevation in heart rate above threshold 120 bpm) was detected in 46% (6 of 13) of participants given 125 mg MDMA during blinded experimental sessions and in none of the participants who received inactive placebo. Heart rate elevation above cut off was seen in 35.3 % (6 of 17) of participants given 125 mg MDMA during open-label experimental sessions. This study is comprised of a small sample, making comparisons with other samples or with healthy controls difficult. The maximum heart rate for any subject receiving MDMA was 140 bpm, observed after 125 mg MDMA during an open-label session. No clinical interventions were required, and no clinically significant AEs were reported based on elevations in heart rate.

Summary of Cardiovascular Effects

The values presented above suggest a dose-dependent action on SBP and heart rate, which is supported in the literature in healthy controls [7, 9, 10, 684]. While peak DBP is higher after doses of 100 mg or greater, very few reports of DBP elevated above cut-off occurred during MDMA administration, suggesting that this is a less common response than elevated SBP or pulse.

On average, cardiovascular vital signs returned to baseline or near-baseline values by final reading, which is the case across all doses of MDMA. Blood pressure and pulse readings permitted the detection of a serious adverse event described in Section 5.3.9, but elevated blood pressure or pulse were not the cause of the event. There are far fewer observations of above threshold values of DBP than SBP. None of the participants have required medical intervention after elevations above cut-off, and the elevations were self-limiting, and none were clinically significant.

5.3.5 Osmoregulatory Effects

The neuroendocrine hormone copeptin, described in Section 5.3.4 Cardiovascular Effects as correlating with AVP in blood, was detected in women acutely after 125 mg MDMA administration [636], and this finding was reproduced in another study reporting that 47.5 mg MDMA caused an acute rise in AVP and a small decrease in plasma sodium, at a time of day when it would not be expected to change, in an all-male sample. [291].

5.3.6 Hepatic Effects

As described in Section 4.4.9, there are case reports of liver disease or hepatotoxicity in ecstasy users, and in vitro and in vivo studies have examined the effects of MDMA on liver function and liver cells. An examination of liver function as assessed approximately one month after MDMA administration in 166 participants, most of them MDMA-naïve, failed to detect any post-drug changes [675]. The first two sponsor-supported Phase 2 studies (MP-1, MP-2) assessed liver function after completion of two or three blinded experimental sessions. Values that differ from established; age-appropriate norms were evaluated for clinical significance. Laboratory assessments of liver function were not conducted after experimental sessions in subsequent sponsor-supported studies and no AEs related to liver function have been reported in these studies.

Table 25: List of All Clinically Significant Changes in Laboratory Values in Two Participants from MP-2

Laboratory Value	Abnormal Test Value	Value at Baseline	Normal Value/Range	Dose
Bilirubin	2.8	2.2	<2.5 mg/dL	125 mg
ESR	32	2.4	<10 mm	125 mg

[1] Post-drug liver panels or other laboratory tests were not conducted in studies subsequent to studies MP-1 and MP-2.

Two participants in the MP-2 study reported two clinically significant abnormalities. One was an elevation in bilirubin in a subject with a family history of elevated bilirubin (probably Gilbert's syndrome), a benign liver condition in which the liver does not properly process bilirubin, with the elevation occurring after open-label treatment with 125 mg to 150 mg initial dose of MDMA Family history of mildly elevated bilirubin is considered an indicator of Gilbert's syndrome. Bilirubin levels can be indicative of decreased liver function, but the liver enzymes were normal at that time, supporting the interpretation that the bilirubin levels were slightly elevated compared to baseline due to hereditary factors. The other abnormal laboratory value, an elevation in erythrocyte sedimentation rate (ESR), a marker of inflammation and not a specific liver function marker, occurred in a subject with a medical history of breast cancer. This value was recorded 3 months after the last administration of MDMA as an AE unrelated to the study drug.

Table 26: Average ALT Values at Baseline and 2-Month Follow-up After Two Experimental Sessions in Participants from MP-1

Timepoint	Placebo	125 mg
Baseline	25.6 (13.4) N=8	22.75 (12.89) N=12 [a]
Primary Endpoint After Two Experimental Sessions	26.4 (13.5) N=8	19.7 (12.7) N=13

[1] Subsequent studies did not measure post-drug liver panels or other laboratory tests.
[a] ALT value for one subject not recorded at baseline.

No clinically significant changes in liver function occurred in MP-1. Values for laboratory tests were within the normal range in MP-1. An independent t-test of differences between baseline and 2-month follow-up alanine aminotransferase (ALT) in placebo and MDMA participants in MP-1 detected a trend toward a change that implied improved liver function that failed to reach statistical significance. Phase 1 studies conducted outside of sponsor support involving administration of MDMA to healthy volunteers have not published any results of liver function after MDMA administration. There have been no reported adverse effects on the liver from these studies.

5.3.7 Neurobiological Effects

The sponsor supported a small BOLD fMRI pilot study investigating brain activity in people with PTSD before and after MDMA-assisted psychotherapy, as a sub-study of 10 participants enrolled in MP-8. Brain activity was recorded while the subject listened to a neutral and a personalized, trauma-related script. Preliminary findings are pending analysis.

Monoamine neurotransmitters are known to modulate sleep architecture and alertness. In a trial with 2 mg/kg MDMA given 6 hours prior to preparing for sleep, MDMA was found to increase Stage 1 sleep and produce fewer periods of REM sleep without increasing daytime sleepiness [323]. Sample size of seven in this study suggests that findings should be accepted with caution. PTSD patients suffer from poor sleep quality. Disturbed REM or non-REM sleep is a contributing factor to maladaptive stress and trauma responses, while a reduction in chronic sleep disruptions from nightmares may be an indicator of efficacy of PTSD treatments. The sponsor is collecting secondary outcomes of sleep quality in PTSD studies with the Pittsburg Sleep Quality Index. Results are pending analysis from studies ongoing at the time of data cutoff.

5.3.8 Neuropsychological Effects

MDMA alters mood, perception, and cognition in healthy volunteers, with effects on emotion and social behavior. At doses of at least 1 mg/kg (approximately 70 mg) and higher, active doses of MDMA alter mood and cognition, and produce slight alterations in perception [11, 598]. Acute subjective effects peak 90 to 120 minutes after oral administration and return to pre-drug levels 3 to 6 hours later [13, 673, 685]. Sub-acute effects assessed in controlled and naturalistic studies may occur 1 to 3 days after drug administration, but are no longer apparent 7 to 14 days later [10, 369, 686]. Most of the therapeutic effects of MDMA are thought to result from changes in affect, cognition, and social interaction. See Section 5.2.3 above for a detailed discussion of neuropsychological effects.

5.3.8.1 Cognitive Functioning

MDMA does not affect responses on tasks requiring attention and response to visual stimuli or visually presented words [13, 28], but has been shown to interfere with performance on digit-symbol substitution - a measure of attention, psychomotor speed and visual memory [8]. A dose of 75 mg improved visual tracking speed, but impaired estimating the position of a blocked (occluded) object in a study of acute effects on skills used for driving cars [685]. A series of studies conducted in the Netherlands examined the effects of MDMA on skills needed for automobile driving reported transient and selective changes in verbal and visual attention, and memory after 75 or 100 mg MDMA [687-690]. MDMA caused difficulty learning or remembering lists of words and difficulty recalling object position within an array of objects. MDMA did not cause impairment in spotting scene changes and reduced weaving in a driving simulation. MDMA was associated with an excessively cautious response to the actions of another car in an assessment of actual driving [691]. While these studies have added to the literature of MDMA's cognitive effects, people in sponsor-supported studies are advised to never operate a vehicle while under the influence of MDMA or any other psychoactive substance.

MDMA acutely improved performance on one measure of impulsivity while failing to affect performance on other impulsivity measures [688]. The causes of these changes are unclear but may relate to changes in attention, salience of visual objects, and altered time perception. Changes in visuospatial recall and driving skills are likely associated with serotonin release or indirect action on serotonin receptors, as the noradrenergic and dopaminergic drug methylphenidate (Ritalin) did not produce similar changes [687, 690, 691]. A study on performance monitoring compared the effects of ethanol, MDMA, and both substances combined, found that MDMA had no effect on performance monitoring and no interaction when ethanol and MDMA are administered concurrently [692]. Administration of a $5HT_{2A}$ receptor antagonist, but not a $5HT_{1A}$ antagonist, reduced impaired performance on a word learning and recall task after MDMA, suggesting that interference is due in part to direct or indirect activation of these receptors [265]. Changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

Acute effects on cognitive function are not assessed in sponsor-supported studies. In three MAPS-sponsored studies, MP-1, MP-4, and MP-12, long-term effect on cognitive function was assessed by administering the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), a relatively brief measure that assesses memory, attention and processing speed, visual-spatial and constructional abilities, and expressive language [693]; and the Paced Auditory Serial Addition Task (PASAT), a measure of auditory processing speed and mental flexibility [694, 695]. These instruments were given prior to and 1 to 2 months after psychotherapy assisted with either full dose MDMA or a comparator/placebo dose.

In MP-1, no significant differences in cognitive function were detected at the 2-month follow-up between subjects who received two sessions with 125 mg of MDMA compared to participants who received placebo, as measured by RBANS and PASAT [43]. These findings suggest that MDMA did not impair cognitive function in this sample or that the effect was too small to attain statistical significance in this small pilot study. Two completed studies (MP-12 and MP-4) include these measures to assess reproducibility of this finding. Available data pooled across studies are presented below by dose.

Table 27: Neurocognitive Function - RBANS Mean Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)	End of Stage 2 Mean (SD)
0 mg	100.9 (15.38) N=10	106.9 (15.15) N=10	---	117.0 (2.83) N=2
40 mg	94.7 (5.20) N=6	104.0 (9.52) N=4	---	103.3 (5.91) N=4
100 mg	95.9 (15.47) N=8	103.4 (13.98) N=9	99.9 (16.50) N=9	---
125 mg	103.2 (15.11) N=30	103.4 (13.21) N=27	99.9 (12.86) N=14	---

On average, RBANS scores trend towards improvement after treatment with placebo and 40 mg to 100 mg initial dose of MDMA, whereas scores stay the same after treatment with 125 mg initial dose of MDMA. The trend towards improvement could be a practice effect from repeated assessments, although stimuli were varied across these, or could possibly be correlated with PTSD symptom reduction. One to three additional treatments with open-label active dose MDMA do not appear to worsen cognitive function based on preliminary End of Stage 1 and End of Stage 2 results. The statistical significance of these pooled findings is yet to be determined.

Table 28: Neurocognitive Function - PASAT Trial 1 and Trial 2 Mean Raw Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12

		PASAT Trial 1		
Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)	End of Stage 2 Mean (SD)
0 mg	42.1 (12.59) N=10	43.7 (12.03) N=10	---	40.0 (4.24) N=2
40 mg	44.3 (9.44) N=6	54.3 (3.86) N=4	---	54.5 (5.51) N=4
100 mg	46.5 (11.56) N=8	48.6 (9.32) N=9	50.2 (9.02) N=9	---
125 mg	45.0 (10.92) N=30	49.4 (8.02) N=27	48.9 (9.21) N=14	---
		PASAT Trial 2		
0 mg	34.2 (11.21) N=10	38.6 (11.66) N=10	---	42.5 (3.54) N=2
40 mg	34.8 (12.12) N=6	44.8 (9.18) N=4	---	45.3 (6.70) N=4
100 mg	33.9 (12.25) N=8	33.1 (14.16) N=9	37.8 (12.33) N=9	---
125 mg	33.3 (9.55) N=30	35.8 (8.33) N=26	36.9 (11.12) N=14	---

On average, PASAT scores stay about the same after treatment with placebo and 100 mg initial dose of MDMA and trend towards improvement after treatment with 40 and 125 mg initial dose of MDMA. The trend towards improvement could be a practice effect from repeated assessments or could be correlated with PTSD symptom reduction. One to three additional treatments with open-label active dose MDMA do not appear to worsen cognitive function and continued to trend towards improvement on average based on preliminary End of Stage 1 and End of Stage 2 results. Cognitive function tests such as the PASAT are also known to be subject to individual variability,

as they require basic proficiency with mathematical skills that are influenced by education level. The significance of these pooled findings is yet to be determined, but it does not appear that MDMA-assisted psychotherapy is negatively impacting cognitive function.

5.3.8.2 Perceptual Effects

MDMA causes slight changes in visual or auditory perception, including changes in the brightness or colors, sounds seeming closer or farther away, and simple visual distortions [7, 8, 10, 11]. Participants also experienced altered time perception, and changes in meaning or significance of perceptions after MDMA [13]. On average, participants maintained insight of their experience, with little indication that MDMA produces any strong alterations to the sense of self or control over the experience [10, 12]. Three healthy volunteers reported developing minimal to mild unusual beliefs or delusions under the influence of 1.5 mg/kg MDMA. According to findings from a study with a small sample (five per group), perceptual alteration may be more pronounced after 2 mg/kg versus 1 mg/kg [673]. These beliefs resolved within a few hours, or by the next day at the latest. These participants were aware that these beliefs were unusual [10]. Women reported experiencing all subjective effects of MDMA more intensely compared to men, but especially those related to perceptual changes [11]. [263, 634]. The effects of MDMA upon perception have not been studied within sponsor-supported studies.

5.3.8.3 Emotional Effects

People receiving active doses of MDMA experience euphoria, positive mood, vigor, and positively experienced derealization, consonant with early retrospective reports, but also report experiencing anxiety, tension, and dysphoria, as well as concern over losing control over the self [8, 10-12]. More surprisingly, participants report increased positive mood even after a dose of 25 mg [251]. It is uncertain whether the increases in positive and negative mood occur simultaneously or at different times throughout the duration of MDMA effects; evidence from two different teams suggests that peaks in negative mood may precede peaks in positive mood [12, 638]. MDMA may have a greater impact on mood in women than in men. Women report greater elevation in negative mood despite similar plasma concentrations of MDMA and metabolites to men [626]. A second dose of MDMA 2 hours after the first does not increase subjective effects beyond that of an initial dose, interpreted by Peiro and colleagues as indications of tolerance to these effects [375]. When two 100 mg doses are given 4 hours apart, most subjective effects are comparable to those after a single dose, despite there being double the amount of plasma MDMA [618]. It is notable that the second dose in this study was identical to the first dose, in contrast to sponsor-supported studies, wherein the second dose is half the size of the initial dose. See section 5.2.3 for further details on subjective effects.

5.3.8.4 Suicidal Ideation, Behavior, and Depression

There is high incidence of positive suicidal ideation and behavior in populations of people with PTSD, especially those suffering from chronic, treatment-resistant PTSD [696, 697]. The FDA has responded to concerns over the occurrence of treatment emergent suicidal ideation or behavior by requiring clinical trials of psychiatric drugs to measure suicidality via the C-SSRS, a clinician-administered guided interview [698]. A score of 4 or 5 on the suicidal ideation category is considered serious, as well as a score of 1 or greater on the behavior category, and individuals with serious ideation or behavior are closely followed until levels return to normal or additional interventions are recommended.

In order to monitor suicidal ideation and behavior after treatment in MAPS-sponsored trials (MP-4, MP-8, MP-9, MP-12, MP16, MP17, MAA-1, MDA-1, and MPVA-1), the C-SSRS is given

repeatedly throughout a study, including lifetime incidence, baseline, before/during/after drug administration, endpoints when other measures are administered, and follow-up visits. Data on suicidal ideation or behavior was not formally measured in the first two sponsor-supported studies (MP-1 and MP-2) or reported in studies of healthy volunteers (MT-1).

Due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event in order to reprocess the memory in a new, less detrimental way, thoughts of ending one's life may surface during this process. However, evidence from clinical studies indicates that these thoughts were most often transient, returned to normal, or even improved following MDMA treatment.

C-SSRS scores have fluctuated during the preparatory sessions (before any drug administration), which is thought to be either a result of discussing traumatic experiences, or participants tapering off long-prescribed medications, such as SSRIs and benzodiazepines, which have been documented elsewhere to induce suicidal ideation or behavior during withdrawal [699-701]. During both non-drug and MDMA-assisted psychotherapy sessions, participants are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with psychotherapy, the distress associated with psychotherapy is unavoidable, and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.

In Tables 29-46 below, suicidal ideation and behavior are summarized for participants in MP-4, MP-8, MP-9, MP-12, MP16, MP17, MPVA-1, MDA-1, and MAA-1 according to suggestions made in the C-SSRS Scoring and Data Analysis Guide [702]. A positive response for suicidal ideation is counted when a subject responds "yes" to any one of the five suicidal ideation questions (Categories 1 to 5) on the C-SSRS (i.e. a score > 0 for suicidal ideation score). Serious suicidal ideation is a suicidal ideation category score of 4 or 5. A positive response for suicidal behavior occurs when a subject responds "yes" to any one of the five suicidal behavior questions (Categories 6 to 10) on the C-SSRS (i.e. a score > 0 for suicidal behavior score). Lifetime scores account for all suicidal ideation and behavior prior to enrollment according to subject recall and medical records. Pre-drug exposure represents measures collected on the Since Last Visit C-SSRS after enrollment during preparatory sessions and before first drug administration in experimental session 1 upon completion of tapering off psychiatric medications. Frequencies are presented as subject counts at each time point. When time points cover multiple visits then percentages are based on the number of observations in which participants would have the opportunity to report.

PTSD

Table 29: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for PTSD Studies MP-4, MP-8, MP-9, and MP-12

		Lifetime [a] N (%)	Pre-drug Exposure [b] N (%)
PTSD			
Blinded Placebo (0 mg)	PI	2 (100.0)	1 (25.0)
	SI	1 (50.0)	0
	PB	1 (50.0)	0
	O	2	4
	N	2	2
Blinded Comparator Doses (25-40 mg)	PI	12 (75.0)	5 (14.3)
	SI	3 (18.8)	0
	PB	5 (31.3)	0
	O	16	35
	N	16	16
Blinded Active Doses (75-125 mg)	PI	45 (90.0)	35 (31.8)
	SI	21 (42.0)	0
	PB	15 (30.0)	1 (0.9)
	O	50	110
	N	50	50

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants

[a] Lifetime accounts for all suicidal ideation and behavior prior to study Visit 1, according to participant recall and medical records.

[b] Pre-drug exposure represents measures taken during Preparatory Sessions and before drug administration in Experimental Session 1.

Table 30: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for PTSD Studies MP-4, MP-8, MP-9, and MP-12

		Session 1 N (%)			Session 2 N (%)			Session 3 N (%)		
		Pre-drug [a]	During-drug [b]	Integration Day 1	Pre-drug [a]	During-Drug[b]	Integration Day 1	Pre-drug [a]	During-drug [b]	Integration Day 1
PTSD										
Blinded	PI	0	0	0	0	0	1 (50.0)	---	---	---
Placebo	SI	0	0	0	0	0	0	---	---	---
(0 mg)	PB	0	0	0	0	0	0	---	---	---
	N	2	2	2	2	2	2	---	---	---
Blinded	PI	1 (6.3)	1 (6.3)	0	0	0	0	1 (50.0)	0	0
Comparator	SI	0	0	0	0	0	0	0	0	0
Doses	PB	0	0	0	0	0	0	0	0	0
(25-40 mg)	N	16	16	15	14	14	14	2	2	2
Blinded	PI	11 (22.0)	4 (8.0)	6 (12.0)	9 (18.8)	9 (18.8)	5 (10.4)	4 (10.5)	6 (15.8)	3 (7.9)
Active Doses	SI	0	0	0	0	0	0	0	0	0
(75-125 mg)	PB	0	0	0	0	0	0	0	0	0
	N	50	50	50	48	50	48	38	38	38
Open-label	PI	0	1 (4.8)	2 (9.5)	1 (4.8)	0	0	1 (20.0)	0	0
Stage 2	SI	0	1 (4.8)	1 (4.8)	0	0	0	0	0	0
Active Dose	PB	0	0	0	0	0	0	0	0	0
(100-125 mg)	N	21	21	21	21	21	21	5	5	18

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

[a] Pre-drug measurement taken day of experimental session prior to drug administration.

[b] During-drug observation measured at experimental session endpoint, approximately 6 hours after drug administration.

Table 31: C-SSRS Positive Responses During Telephone Contact Following Experimental Sessions for PTSD Studies MP-4, MP-8, MP-9, MP-12

		Session 1 N (%)		Session 2 N (%)		Session 3 N (%)	
		Day 2	Day 7	Day 2	Day 7	Day 2	Day 7
PTSD							
Blinded Placebo (0 mg)	PI	0	0	0	0	---	---
	SI	0	0	0	0		
	PB	0	0	0	0		
	N	2	2	2	2		
Blinded Comparator Doses (25-40 mg)	PI	0	0	0	0	0	0
	SI	0	0	0	0	0	0
	PB	0	0	0	0	0	0
	N	16	16	14	14	4	4
Blinded Active Doses (75-125 mg)	PI	7 (14.3)	10 (20.4)	12 (25.5)	8 (17.0)	5 (13.5)	5 (13.5)
	SI	0	0	0	1 (2.1)	0	1 (2.7)
	PB	0	0	0	0	0	0
	N	49	49	47	47	37	37
Open-label Stage 2 Doses (100-125 mg)	PI	3 (15.8)	0	1 (4.8)	0	0	0
	SI	2 (10.5)	0	0	0	0	0
	PB	0	0	0	0	0	0
	N	19	19	21	19	17	18

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

Table 32: C-SSRS Positive Responses at Endpoints After Treatment for PTSD Studies MP-4, MP-8, MP-9, and MP-12

		Primary/ Secondary Endpoint N (%)	End of Stage 1/ End of Stage 2 N (%)	Long-term Follow-up N (%)
PTSD				
Blinded Placebo (0 mg)	PI	0	---	1 (50.0)
	SI	0		0
	PB	0		0
	N	2		2
Blinded Comparator Doses (25-40 mg)	PI	1 (8.3)	0	1 (7.7)
	SI	0	0	0
	PB	0	0	0
	N	12	2	13
Blinded Active Doses (75-125 mg)	PI	15 (34.9)	11 (28.9)	13 (27.7)
	SI	2 (4.7)	0	1 (2.1)
	PB	0	0	0
	N	43	38	47
Open-label Stage 2 Doses (100-125 mg)	PI	0	1 (5.6)	---
	SI	0	0 (0)	
	PB	0	0 (0)	
	N	9	18	

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

In a PTSD sample with prevalent lifetime history of suicidal ideation, participants randomized to either dose group reported pre-drug suicidal ideation in blinded experimental sessions. More active dose participants reported pre-drug positive ideation. During experimental and integrative sessions, the active dose group reported positive ideation more frequently than the control group or open-label crossover group; however, pre-drug counts were also greater in the active dose group. The difference

between groups could be random or could be possibly due to MDMA or trauma-memory recall during psychotherapy. No participants reported positive suicidal behavior, and two reports of serious ideation occurred during and the day following the first open-label MDMA session. Reports of positive ideation during the telephone calls conducted during the week after experimental sessions for participants randomized to active dose MDMA (13.5-25.5%) was greater than the control group (0%). Prevalence increased after the second experimental session as seen during experimental sessions, likely due to enhancement of the therapeutic process with each exposure bringing up traumatic memories. Since MDMA is only administered in the context of psychotherapy, and PTSD participants have a lifetime history of suicidal ideation, these effects were expected. About a third of active dose PTSD participants and one comparator dose PTSD subject experienced suicidal ideation at the primary endpoint (1 month after MDMA administration), with two participants in the active dose group experiencing serious ideation. The prevalence of suicidal ideation remained consistent with end of treatment rates at long-term follow-up and was reduced compared to life-time prevalence.

Table 33: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for Study MPVA-1

		Lifetime [a] N (%)	Pre-drug Exposure [b] N (%)
CBCT & MDMA-assisted Psychotherapy in Dyads			
PTSD+	PI	6 (100.0)	3 (25.0)
Open-label	SI	6 (100.0)	0
(75-100 mg)	PB	4 (66.7)	0
	O	6	12
	N	6	6
CSO	PI	3 (50.0)	1 (8.3)
Open-label	SI	0	0
(75-100 mg)	PB	0	0
	O	6	12
	N	6	6

PTSD+ = PTSD diagnosis present, CSO = Concerned Significant Other, PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants

[a] Lifetime accounts for all suicidal ideation and behavior prior to study Visit 1, according to participant recall and medical records.

[b] Pre-drug exposure represents measures taken during Preparatory Sessions and before drug administration in Experimental Session 1.

Table 34: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for Study MPVA-1

		Session 1 N (%)			Session 2 N (%)		
		Pre-drug [a]	During-drug [b]	Integration Days [c]	Pre-drug [a]	During-drug [b]	Integration Days [d]
PTSD+	PI	3 (50.0)	0	2 (33.3)	0	0	1 (16.7)
Open-label	SI	0	0	0	0	0	0
(75-100 mg)	PB	0	0	0	0	0	0
	N	6	6	6	6	6	6
CSO	PI	1 (16.7)	0	0	0	0	0
Open-label	SI	0	0	0	0	0	0
(75-100 mg)	PB	0	0	0	0	0	0
	N	6	6	6	6	6	6

PTSD+ = PTSD diagnosis present, CSO = Concerned Significant Other,
PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

[a] Pre-drug measurement taken day of experimental session prior to drug administration.
[b] During-drug observation measured at experimental session endpoint, approximately 6 hours after drug administration.
[c] Integration Days represents visits 4 to 8 and phone contacts.
[d] Integration Days represents visits 11 to 15 and phone contacts.

Table 35: C-SSRS Positive Responses at Endpoints After Treatment for Study MPVA-1

		Midpoint N (%)	Primary Endpoint N (%)	3-Month Follow-up N (%)	12-Month Follow-up N (%)
CBCT & MDMA-assisted Psychotherapy in Dyads					
PTSD+	PI	2 (33.3)	0	2 (33.3)	0
Open-label	SI	0	0	0	0
(75-100 mg)	PB	0	0	0	0
	N	6	6	6	6
CSO	PI	0	0	0	0
Open-label	SI	0	0	0	0
(75-100 mg)	PB	0	0	0	0
	N	6	6	6	6

PTSD+ = PTSD diagnosis present, CSO = Concerned Significant Other, PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

In the open-label MPVA1 study, more PTSD participants (50.0%) experienced positive ideation before MDMA dosing than the concerned significant other (16.7%). There were no positive ideation reports for either group during MDMA sessions. During the days following an MDMA session, the PTSD group had greater frequency of positive ideation (16.7-33.3%) compared to the CSO group (0%), with no serious ideation or behavior.

Table 36: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for PTSD Studies MP16 and MP17 as of October 1, 2018

		Lifetime [a] N (%)	Pre-drug Exposure [b] N (%)
PTSD			
Open-label	PI	27 (96.4)	10 (35.7)
(80-120 mg)	SI	10 (35.7)	0
	PB	12 (42.9)	1 (3.6)
	O	28	28
	N	28	28

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants
[a] Lifetime accounts for all suicidal ideation and behavior prior to study Visit 1, according to participant recall and medical records.
[b] Pre-drug exposure represents measures taken during a Preparatory Session.

Table 37: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for Studies MP16 and MP17

		Session 1 N (%)			Session 2 N (%)			Session 3 N (%)		
		Pre-drug [a]	During-drug [b]	Integration Day 1	Pre-drug [a]	During-Drug[bB]	Integration Day 1	Pre-drug [a]	During-drug [b]	Integration Day 1
PTSD										
Open-label	PI	8 (28.6)	1 (3.6)	1 (3.6)	2 (7.1)	1 (3.6)	1 (3.6)	1 (3.6)	0	0
Active Dose	SI	0	0	0	0	0	0	0	0	0
(80-120 mg)	PB	0	0	0	0	0	0	0	0	0
	N	28	28	28	28	28	28	28	28	28

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

[a] Pre-drug measurement taken day of experimental session prior to drug administration.

[b] During-drug observation measured at experimental session endpoint, approximately 6 hours after drug administration.

Table 38: C-SSRS Positive Responses During Telephone Contact Following Experimental Sessions for Studies MP16 and MP17

		Session 1 N (%)		Session 2 N (%)		Session 3 N (%)	
		Day 2	Day 7	Day 2	Day 7	Day 2	Day 7
PTSD							
Open-label	PI	2 (7.1)	4 (14.3)	1 (3.6)	4 (14.3)	1 (3.6)	2 (7.1)
Active Doses	SI	0	0	0	1 (3.6)	0	0
(80-120 mg)	PB	0	0	0	0	0	0
	N	28	28	28	28	28	28

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

Table 39: C-SSRS Positive Responses at Endpoints After Treatment for Studies MP16 and MP17

		Study Termination N (%)
Open-label (80-120 mg)	PI	1 (5.6)
	SI	0
	PB	0
	N	18

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

Based on lifetime results, most participants with PTSD had a history of suicidal ideation. In the PTSD sample, 18.8-100.0% of participants had a history of serious ideation and 30.0-66.7% had positive behavior, which is consistent with the literature [703]. Two PTSD participants in the active dose group exhibited suicidal behavior after enrollment but prior to any MDMA administration. Post drug, during MDMA sessions and the month following, positive ideation was reported by 3.6-14.3% of participants, with one account of serious ideation (3.6%), and no positive behavior that occurred post drug. At study termination, one subject reported positive ideation, with overall fewer participants experiencing suicidal ideation and behavior than prior to study participation.

Social Anxiety in Autistic Adults

Table 40: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for Study MAA-1

		Lifetime [a] N (%)	Pre-drug Exposure [b] N (%)
Social Anxiety in Autistic Adults			
Blinded Placebo (0 mg)	PI	3 (75.0)	0
	SI	0	0
	PB	1 (25.0)	0
	O	4	8
	N	4	4
Blinded Active Doses (75-125 mg)	PI	4 (50.0)	0
	SI	1 (12.5)	0
	PB	1 (12.5)	0
	O	8	16
	N	8	8

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants
[a] Lifetime accounts for all suicidal ideation and behavior prior to study Visit 1, according to participant recall and medical records.
[b] Pre-drug exposure represents measures taken during Preparatory Sessions and before drug administration in Experimental Session 1.

Table 41: C-SSRS Positive and Serious Responses During Experimental Sessions and Integration Session 1, Day 2 Phone Call, and Day 7 Phone Call Post-Drug for Study MAA-1

Dose		Session 1 N (%)					Session 2 N (%)				
		Pre-drug [a]	During-drug [b]	Integration Session 1	Day 2	Day 7	Pre-drug [a]	During-drug [b]	Integration Session 1	Day 2	Day 7
Social Anxiety in Autistic Adults											
Blinded	PI	0	0	0	0	0	0	0	0	0	0
Placebo	SI	0	0	0	0	0	0	0	0	0	0
(0 mg)	PB	0	0	0	0	0	0	0	0	0	0
	N	4	4	4	4	3	3	3	4	4	4
Blinded	PI	0	1 (14.3)	1 (12.5)	0	0	0	0	0	0	0
Active Dose	SI	0	0	0	0	0	0	0	0	0	0
(75-125 mg)	PB	0	0	0	0	0	0	0	0	0	0
	N	8	7	8	8	8	8	6	7	7	7
Open-label	PI	1 (25.0)	0	0	0	0	0	0	0	0	0
Stage 2	SI	0	0	0	0	0	0	0	0	0	0
Active Dose	PB	0	0	0	0	0	0	0	0	0	0
(75-125 mg)	N	4	4	4	4	4	4	3	4	4	3

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

[a] Pre-drug measurement taken day of experimental session prior to drug administration.

[b] During-drug observation measured at experimental session endpoint, approximately 6 hours after drug administration.

Table 42: C-SSRS Positive Responses at Endpoints After Treatment for Study MAA-1

		Primary/ Secondary Endpoint N (%)	Long-term Follow-up N (%)
Social Anxiety in Autistic Adults			
Blinded	PI	1 (25.0)	2 (50.0)
Placebo	SI	0	0
(0 mg)	PB	0	0
	N	4	4
Blinded	PI	2 (28.6)	0
Active Doses	SI	0	0
(75-125 mg)	PB	0	0
	N	7	7

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

In the MDMA study in autistic adults, 0-12.5% of participants had a history of serious suicidal ideation and 12.5-25.0% reported suicidal behavior. During the preparatory phase prior to blinded drug administration, there were no reports of suicidal ideation or behavior. There was one report of positive ideation on the day of an MDMA session, and one on the day following. At endpoints, 25.0-50.0% had positive ideation. Two participants reported positive ideation, although not serious, during follow-up which may have resulted from ending the therapeutic relationship. These participants were transitioned to non-study therapists and went back on psychiatric medications under the care of their prescribing physician. No serious ideation or behavior occurred during the study. Generally, rates of suicidal thoughts were lower in this population than the PTSD sample.

Anxiety Associated with a Life-threatening Illness

Table 43: Summary of Lifetime and Baseline Positive and Serious Responses on C-SSRS for Study MDA-1

		Lifetime [a] N (%)	Pre-drug Exposure [b] N (%)
Anxiety Associated with a Life-threatening Illness			
Blinded	PI	4 (80.0)	5 (25.0)
Placebo	SI	1 (20.0)	0
(0 mg)	PB	0	1 (5.0)
	O	5	20
	N	5	5
Blinded	PI	10 (76.9)	0
Active Dose	SI	0	0
(125 mg)	PB	3 (23.1)	0
	O	13	52
	N	13	13

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, O=Observations, N=Number of Participants
[a] Lifetime accounts for all suicidal ideation and behavior prior to study Visit 1, according to participant recall and medical records.
[b] Pre-drug exposure represents measures taken during Preparatory Sessions and before drug administration in Experimental Session 1.

Table 44: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for Study MDA-1

Dose		Session 1 N (%)			Session 2 N (%)			
		Pre-drug [a]	During-drug [b]	Integration Day 1	Pre-drug [a]	During-drug [b]	Integration Day 1	Pre-drug [a]
Anxiety Associated with a Life-threatening Illness								
Blinded Placebo (0 mg)	PI	0	0	0	0	0	0	---
	SI	0	0	0	0	0	0	
	PB	0	0	0	0	0	0	
	N	5	5	5	5	5	5	
Blinded Active Dose (125 mg)	PI	0	0	0	0	0	0	0
	SI	0	0	0	0	0	0	0
	PB	0	0	0	0	0	0	0
	N	13	13	13	13	13	13	11
Open-label Stage 2 Active Dose (125 mg)	PI	0	0	0	0	0	0	0
	SI	0	0	0	0	0	0	0
	PB	0	0	0	0	0	0	0
	N	5	5	5	5	5	5	5

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

[a] Pre-drug measurement taken day of experimental session prior to drug administration.

[b] During-drug observation measured at experimental session endpoint, approximately 6 hours after drug administration.

Table 45: C-SSRS Positive Responses During Telephone Contact Following Experimental Sessions for Study MDA-1

		Session 1 N (%)		Session 2 N (%)		Session 3 N (%)	
		Day 2	Day 7	Day 2	Day 7	Day 2	Day 7
Anxiety Associated with a Life-threatening Illness							
Blinded Placebo (0 mg)	PI	0	0	0	0	---	---
	SI	0	0	0	0		
	PB	0	0	0	0		
	N	5	5	5	5		
Blinded Active Dose (125 mg)	PI	0	0	0	0	0	0
	SI	0	0	0	0	0	0
	PB	0	0	0	0	0	0
	N	13	13	13	13	12	12
Open-label Stage 2 Doses (100-125 mg)	PI	0	0	0	0	0	0
	SI	0	0	0	0	0	0
	PB	0	0	0	0	0	0
	N	5	5	5	5	5	5

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

Table 46: C-SSRS Positive Responses at Endpoints After Treatment for Study MDA-1

Dose		Primary/ Secondary Endpoint N (%)	End of Stage 1/ End of Stage 2 N (%)	Long-term Follow-up N (%)
Anxiety Associated with a Life-threatening Illness				
Blinded Placebo (0 mg)	PI	0	---	1 (20.0)
	SI	0		0
	PB	0		0
	N	5		5
Blinded Active Dose (125 mg)	PI	1 (7.7)	0	0
	SI	0	0	0
	PB	0	0	0
	N	13	12	12
Open-label Stage 2 Doses (100-125 mg)	PI	0	0	---
	SI	0	0	
	PB	0	0	
	N	5	5	

PI=Positive Ideation, SI=Serious Ideation, PB=Positive Behavior, N=Number of Participants

In participants with a life-threatening illness, 0-20.0% of participants had a history of serious suicidal ideation and 0-23.1% reported suicidal behavior. During the preparatory phase prior to blinded drug administration, one participant experienced suicidal behavior, and 25.0% had positive ideation. There were no reports of suicidal ideation or behavior during the preparatory sessions or during the treatment period. One occurrence of positive ideation was recorded at the primary endpoint and long-term follow-up.

Summary of Suicidal Ideation and Behavior Across Populations and Indications

As of 12 June 2019, three cases of suicidal ideation and four cases of suicidal behavior were deemed serious across sponsor-supported Phase 2 and Phase 3 studies. Suicidal ideation was reported in a participant in study MP-8, reported 6 days after treatment with 30 mg MDMA and lasted 6 days, concurrent with increased depressive symptoms triggered by external trauma cues, and was treated with prescription medication and hospitalization. The participant who experienced suicidal ideation later experienced depression that was rated serious and unrelated to the study drug, with the event occurring approximately nine months after a final experimental session. The episode resolved approximately three weeks after it developed. Depression in this subject was rated severe. The depression led to hospitalization, and the participant reported full recovery after the episode. . In an extension to study MP-1 involving a single, additional administration of 125 mg MDMA for participants exhibiting relapse after completing the study, a participant was hospitalized with major depressive episode and suicidal ideation nine months after the additional experimental session, and fully recovered after this episode. In MAPP1, one participant was hospitalized 9 days after the blinded experimental session for expressing a worsening feeling of not wanting live and with no plan or intent of self-harm. The participant was prescribed Lexapro by the hospital doctor, released from hospital, and reported feeling better. Four serious adverse events of suicidal behavior occurred across MAPS-supported studies. Two events were reported for one participant in the ongoing, placebo-controlled study MAPP1, and one event in one person in the open-label study MP16, and one in study MP-2. In MP-2, prior to the collection of formal suicidal ideation with C-SSRS, one participant was hospitalized for suicidal behavior that allegedly developed after a conflict with her ex-husband two weeks prior to drug administration, indicating that suicidal ideation and behavior can occur at baseline prior to drug administration. This subject fully recovered and went on to participate in the study. In the case occurring in MP16, the therapists learned of a recent suicide attempt during an integration session, possibly arising from apprehension about the study ending. The participant was admitted to the ER overnight, and fully recovered in the subsequent day. In the first of the two events in the participant in the ongoing, placebo-controlled MAPP1 study, the participant ingested a combination of over the counter medications, and acknowledged suicidal ideation, but followed instructions not to consume alcohol. This was considered an occurrence of testing the therapists, but after discussion was coded as a suicide attempt. The second event occurred two months later, still within the blinded session.

Overall the incidence of serious suicidal ideation or behavior in sponsor-supported studies was low, fluctuating in some participants post treatment with MDMA and psychotherapy, and returning to category 1-3 suicidal ideation scores while participants were closely monitored. Given that severe PTSD sufferers are known to experience suicidal ideation and behavior, it is difficult to identify a single cause of the increase in suicidal thinking or behavior (i.e. exacerbation of PTSD symptoms, MDMA-stimulated effects, or processing of traumatic memories during psychotherapy with MDMA). A large percentage of people enrolled in the studies reported suicidal ideation and behavior during sometime in their lives prior to study enrollment, which may reflect a manifestation of PTSD or co-morbid affective disorders. When positive serious ideation or behavior occurred after enrollment, the investigators made follow-up observations of C-SSRS to ensure subject safety, and tracked scores until they returned to non-

serious levels. Frequency of ideation and behavior was greater in the PTSD population compared to healthy individuals, autistic adults, and people with life-threatening illnesses.

Beck Depression Inventory-II

PTSD

The Beck Depression Inventory-II (BDI-II) is a widely used self-administered measure of depression and includes an item on suicidal ideation. Participants' depression levels were evaluated at baseline and at endpoints throughout the study, as a secondary measure of effectiveness of treatment. Tables 47 through 51 below show mean BDI-II scores for participants in MP-4, MP-8, MP-9, MP-12, MAA-1, MDA-1, MPVA-1, MP16, and MP17. Scores of 13 or lower indicate minimal, 14 to 19 mild, 20 to 28 moderate, 29 and above indicate severe depression symptoms.

Table 47: Mean BDI-II Scores at Baseline and Endpoints by Dose for Studies MP-4, MP-8, MP-9, and MP-12

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)
Blinded (0-40 mg)	26.1 (10.57) N=18	20.1 (10.39) N=18	17.0 (21.21) N=2
Blinded (75-125 mg)	30.2 (11.56) N=50	15.7 (13.40) N=49	11.0 (10.24) N=36
Open-label (125 mg)	35.0 (19.80) N=2	18.0 (22.63) N=2	---
Dose Stage 2	**Secondary Endpoint Mean (SD)**	**End of Stage 2 Mean (SD)**	**12-month Follow-up Mean (SD)**
Open-label (100-125 mg)	11.1 (9.75) N=19	13.7 (12.84) N=19	---
All Participants	---	---	11.7 (10.38) N=61

As depression is not the primary indication in sponsor-supported studies, only a subset of participants presented clinically significant co-morbid depression at baseline, which contributes to variation within each dose group. Scores trend downward in most active MDMA dose groups, indicating an improvement in depression symptoms on average.

Stage 2 crossover data, after initial treatment with placebo or comparator, show that depression scores were in the minimal to mild range on average after active dose treatment. All participants receive active dose treatments in either Stage 1 or Stage 2 before data were collected at 12-month follow-up in PTSD studies. On average, depression scores remained in the minimal to mild range at 12-month follow-up, suggesting improvements in depression observed during treatment were durable on average.

Table 48: Mean BDI-II Scores at Baseline and Endpoints by Group for Study MPVA-1

Dose	Baseline Mean (SD)	Midpoint Mean (SD)	Primary Endpoint Mean (SD)	3-month Follow-up Mean (SD)	6-month Follow-up Mean (SD)
PTSD+ Open-label (75-100 mg)	32.8 (8.75) N=6	19.7 (17.56) N=6	11.6 (16.88) N=5	11.7 (12.99) N=6	7.3 (9.93) N=6
CSO Open-label (75-100 mg)	4.3 (4.63) N=6	4.3 (3.01) N=6	6.2 (7.98) N=5	3.0 (4.15) N=6	3.5 (4.28) N=6

PTSD+ = PTSD diagnosis present, CSO = Concerned Significant Other

Participants with PTSD had severe depression on average at study start, with symptoms improving across the treatment period. The CSO group (healthy individuals) had minimal depression symptoms at baseline, and stayed approximately the same across the study.

Table 49: Mean BDI-II Scores at Baseline and Endpoints for Study for Studies MP16 and MP17 as of October 1, 2018

Dose	Baseline Mean (SD)	Study Termination Mean (SD)
Open-label (80-120 mg)	32.8 (14.01) N=27	7.2 (9.21) N=18

In MP16 and MP17, the BDI-II was administered only at baseline and at the study termination visit. BDI-II scores dropped on average of 25.6 points at study end, indicating marked improvement in depression symptoms after three MDMA sessions.

Social Anxiety in Autistic Adults

Table 50: Mean BDI-II Scores at Baseline and Endpoints by Dose for Study MAA-1

Dose	Baseline Mean (SD)	1 Day Post Session 1 Mean (SD)	2 Weeks Post Session 1 Mean (SD)	1 Month Post Session 1 Mean (SD)
Placebo	17.0 (16.51) N=4	2.3 (1.50) N=4	4.8 (5.85) N=4	8.3 (11.79) N=4
MDMA (75-125 mg)	16.3 (12.65) N=8	4.9 (3.00) N=8	9.6 (9.2) N=8	14.7 (15.79) N=7
Dose		**1 Day Post Session 2 Mean (SD)**	**2 Weeks Post Session 2 Mean (SD)**	**1 Month Post Session 2 Mean (SD)**
Placebo	---	1.8 (2.87) N=4	2.5 (5.00) N=4	3.8 (7.50) N=4
MDMA (75-125 mg)	---	7.0 (3.37) N=7	6.0 (5.39) N=7	6.3 (6.45) N=7

MDMA did not worsen symptoms of depression in people exhibiting moderate to severe co-morbid depression, and may have had an acute antidepressant effect. In most cases, symptom scores declined or remained at similar levels after MDMA-assisted psychotherapy. Some participants experienced transient positive suicidal ideation during treatment, with these scores declining throughout the course of psychotherapy, as discussed in Section 5.3.8.5 Suicidal Ideation, Behavior, and Depression above. In sum, C-SSRS findings do not suggest a general

increase in suicidality, and improvements in depression scores indicate that MDMA-assisted psychotherapy did not exacerbate or induce symptoms of suicidality or depression.

Anxiety Associated with Life-threatening Illness

Table 51: Mean BDI-II Scores at Baseline and Endpoints by Dose for Study for Study MDA-1

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)	
Blinded (0 mg)	30.0 (11.4) N=5	15.4 (9.86) N=5	---	---
Blinded (125 mg)	30.2 (11.02) N=13	9.3 (10.38) N=13	2.7 (1.78) N=12	---
Dose Stage 2	**Secondary Endpoint Mean (SD)**	**End of Stage 2 Mean (SD)**	**6-month Follow-up Mean (SD)**	**12-month Follow-up Mean (SD)**
Open-label (125 mg)	6.0 (5.52) N=5	3.8 (3.96) N=5	---	---
All Participants	---	---	3.2 (3.06) N=16	4.3 (4.03) N=17

In individuals with anxiety associated with life-threatening illness, baseline BDI-II scores on average, indicated severe depression. After treatment, depression symptoms improved in both the MDMA and placebo group, with greater improvement in the MDMA group. Depression symptoms were on average minimal by the long-term follow-up visits.

5.3.9 Adverse Events

5.3.9.1 Commonly Reported Adverse Events

Common AEs of MDMA reported in non-sponsor supported Phase 1 studies in healthy volunteers include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils [8-11]. Some reports indicated decreased rather than increased alertness [8]. Other common AEs reported in controlled studies of MDMA include reduced appetite, dizziness, tight jaw, bruxism (tooth-grinding), disturbance in attention, impaired gait or balance, dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or recall [13], and unusual thoughts or ideas [10]. Other less commonly reported events include paraesthesia (unusual body sensations) such as tingling, or feeling hot or cold. MDMA can produce anxiety in healthy volunteers [10, 11, 13]. These effects are transient and recede as drug effects wane. One study found that women were more likely than men to experience the most commonly reported adverse effects of MDMA, though men were more likely than women to experience the specific AEs of nausea and sweating [11]. Kirkpatrick and colleagues examined a pooled sample of 220 healthy volunteers from three laboratories and failed to find gender differences in subjective or cardiovascular effects [684].

The most commonly reported AEs from Phase 1 studies published between 1986 and 2012 were used to develop a list of common reactions, or Spontaneously Reported Reactions, to record daily occurrence, duration and severity [10, 13, 28, 51, 70, 229, 232, 596, 630, 634, 635, 638]. Based on the reports summarized in Table 52, 24 reactions were identified to be tracked during sponsor-supported studies MP-1 and MP-2, and three were added after examining data from the first sponsor-supported study in a PTSD sample (MP-1). The investigators noted that participants in

MP-1 reported greater incidence of diarrhea and muscle tightness, which were added to the list, and further observation led to the addition of impaired judgment. Based on the half-life of active MDMA doses being seven to nine hours, it was most important to collect reactions on the day of drug administration and the following seven days after each experimental session. The subset of AEs referred to as spontaneously reported reactions included: anxiety, depressed mood, insomnia, obsessive rumination, restlessness, irritability, headache, disturbance in attention, dizziness, parasthesia, judgment impaired, hypersomnia, nausea, diarrhea, fatigue, asthenia, feeling cold, muscle tension, decreased appetite, hyperhidrosis, disturbed gait, dry mouth, thirst, sensation of heaviness, somnolence, and nystagmus. Table 52 summarizes the frequency of reactions after MDMA in various Phase 1 studies not sponsored by MAPS, cited above.

Table 52: Mean Prevalence of Commonly Reported Reactions by Verbatim and Preferred Term During MDMA or Placebo Treatment Collected from 12 Phase 1 Studies Conducted Outside of Sponsor Support

Treatment Group		**Placebo**	**MDMA**		
Participants		N=57	N=174		
Reaction	**Preferred Term**	**Mean%**	**Mean%**	**Min%**	**Max%**
Anxiety	Anxiety	0%	19%	14%	50%
Difficulty concentrating	Disturbance in attention	16%	53%	3%	88%
Dizziness	Dizziness	2%	43%	21%	75%
Drowsiness	Somnolence	50%	26%	14%	50%
Dry mouth	Dry mouth	N/A	64%	57%	88%
Fatigue	Fatigue	26%	15%	7%	50%
Feeling cold	Feeling cold	4%	43%	23%	75%
Weakness	Asthenia	0%	16%	3%	36%
Headache	Headache	0%	11%	0%	50%
Heavy legs	Sensation of heaviness	0%	38%	38%	38%
Impaired balance/gait	Disturbed gait	0%	44%	10%	71%
Insomnia	Insomnia	0%	17%	0%	31%
Jaw clenching/tight	Muscle tightness (jaw)	0%	60%	44%	76%
Lack of appetite	Decreased appetite	2%	68%	50%	97%
Lack of energy	Decreased energy	14%	14%	3%	50%
Muscle ache/tension	Muscle tightness	N/A	20%	0%	50%
Nausea	Nausea	4%	21%	8%	36%
Nystagmus	Nystagmus	N/A	23%	3%	80%
Parasthesia	Parasthesia	0%	22%	3%	75%
Ruminations	Obsessive ruminations	23%	38%	38%	38%
Perspiration	Hyperhidrosis	0%	40%	0%	50%
Restlessness	Restlessness	0%	46%	29%	69%
Sensitivity to cold	Feeling cold	7%	38%	38%	38%
Thirst	Thirst	4%	48%	38%	63%
Restless legs	Restless legs syndrome	0%	45%	44%	46%
Palpitations	Palpitations	0%	37%	21%	63%
Hot flashes	Feeling hot	0%	23%	23%	23%
Trismus	Trismus	N/A	21%	3%	57%
Inner tension	Tension	0%	18%	3%	50%
Urge to urinate	Micturition urgency	8%	15%	15%	15%
Tremor	Tremor	0%	22%	3%	56%
Forgetfulness	Memory impairment	0%	15%	3%	38%
Brooding	Obsessive rumination	0%	12%	3%	29%

In sponsor-supported Phase 2 studies, researchers recorded any spontaneous (unsolicited) reports of common reactions on the day of each experimental session and 7 days after. The same severity coding system for AEs was employed throughout all studies, based on limitation in daily function. Tables 53-54 below display data from studies investigating MDMA-assisted psychotherapy for PTSD (MP-1, MP-2, MP-4, MP-8, MP-9 and MP-12), social anxiety in autistic adults (MAA-1), and anxiety associated with life-threatening illness (MDA-1).

PTSD

The 125 mg MDMA dose was tested in the largest sample of blinded participants among MDMA doses (N=58). Therefore, incidence of AEs was most representative of AEs anticipated from Phase 3 studies in this dose group as described below. Among spontaneously reported reactions (Table 53), only nausea (6.9%), tight jaw (5.2%), dizziness (3.4%), fatigue (3.4%), and increased irritability (1.7%) were rated as severely limiting normal daily function in the 125 mg MDMA dose group, but not in the placebo or comparator dose groups (25-40 mg MDMA). During blinded experimental sessions, the most frequently reported unsolicited reactions at any severity for the 125 mg MDMA dose group were: tight jaw (63.8% MDMA vs. 30% placebo), lack of appetite (50% MDMA vs. 20% placebo), dizziness (50% MDMA vs. 20% placebo), and nausea (43.1% MDMA vs. 30% placebo). Consistent with known thermoregulatory and osmoregulatory effects of MDMA, reactions including sensitivity to cold (39.7% MDMA vs. 20% placebo), perspiration (32.8% MDMA vs. 10% placebo), thirst (29.3% MDMA vs. 10% placebo), and dry mouth (24.1% MDMA vs. none in placebo) were noted. In addition, anxiety (70% MDMA vs. 90% placebo), headache (51.7% MDMA vs. 80% placebo), fatigue (48.3% MDMA vs. 70% placebo), low mood (20.7% MDMA vs. 20% placebo), and insomnia (34.5% MDMA vs. 90% placebo) were also reported but with comparable or higher incidence in the placebo group vs. 125 mg MDMA. Comparator dose groups (25-40 mg MDMA) reported reactions at a comparable rate to placebo dose groups. The small sample size of the placebo group presents challenges for interpretation of relative incidence of reactions. However overall typical reactions were not long-lasting, nor did they warrant cause for clinical concern. Elevations in anxiety and poor sleep were managed across dose groups with short-acting low dose benzodiazepine, or sleep aids as needed, per clinical judgment of the study physician.

During the 7-day safety window, reactions were much less frequently reported (Table 54). Reactions that were more frequently reported in the active dose group during the week after drug administration include a range of incidences over 7 days: lack of appetite (8.1%-28.4% of active dose participants vs. none of placebo), tight jaw (2.7%-25.7% of active dose participants vs. 20.0% of placebo only on Day 1), restlessness (4.1%-10.8% of active dose participants vs. none of placebo), weakness (2.7%-9.5% of active dose participants vs. none of placebo), dry mouth (1.4%-9.5% of active dose participants vs. none of placebo), thirst (1.4%-6.8% of active dose participants vs. none of placebo), sensitivity to cold (1.4%-4.1% of active dose participants vs. none of placebo), heavy legs (1.4%-4.1% of active dose participants vs. none of placebo), and impaired gait/balance (1.4%-5.4% of active dose participants vs. 10.0% of placebo only on Day 3). The only notable reaction predominantly reported by the comparator dose group was muscle tension during the week following experimental sessions (12.5%-25.0%), which was only reported transiently and by fewer participants in the active dose group (2.0%-8.0%), and not at all by the placebo group. Anxiety, fatigue, headache, nausea, needing more sleep, increased irritability, difficulty concentrating, ruminations, and low mood were reported at comparable rates across MDMA and placebo groups.

In summary, spontaneously reported reactions were typically observed during drug administration, but are transient and diminish as the drug is metabolized and excreted over the next 24 hours, with the majority of reactions resolving within several days and up to one week after dosing. Among spontaneous reports of reactions to MDMA, anxiety, muscle tightness in the jaw, lack of appetite, dizziness, and nausea were most commonly reported acutely during MDMA-assisted psychotherapy. During the week following treatment, the most frequently reported reactions attributable to MDMA based on relative incidence were lack of appetite, muscle tightness in the jaw, restlessness, weakness, dry mouth, thirst, impaired gait/balance, sensitivity to cold. Severe anxiety, insomnia, fatigue, and depressed mood are commonly reported in PTSD studies in both placebo and MDMA groups. Reactions were generally mild and not clinically alarming. Given the benign safety profile and positive efficacy signal, the sponsor concludes that the risk-benefit analysis of MDMA-assisted psychotherapy weighs in favor of expanding trials to enroll a larger number of participants in placebo-controlled Phase 3 trials to continue evaluation of safety versus efficacy for this treatment.

Table 53: Prevalence of Spontaneously Reported Reactions at Any Severity During Experimental Sessions in Sponsor-Supported Phase 2 PTSD Studies of MDMA-Assisted Psychotherapy MP-1, MP-2, MP-4, MP-9, MP-8, MP-12 (N=105)

Dose	0 mg (N=10)	25 mg (N=8)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100 mg (N=9)	125 mg (N=58)	Open-label (N=78)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Anxiety	9 (90.0)	2 (25.0)	4 (57.1)	2 (33.3)	5 (71.4)	6 (66.7)	41 (70.7)	38 (48.7)
Severe	4 (40.0)	---	1 (14.3)	---	1 (14.3)	1 (11.1)	3 (5.2)	8 (10.3)
Diarrhea[a]	---	---	---	---	---	---	---	3 (3.8)
Severe	---	---	---	---	---	---	---	---
Difficulty Concentrating	1 (10.0)	---	2 (28.6)	1 (16.7)	1 (14.3)	3 (33.3)	12 (20.7)	14 (17.9)
Severe	---	---	---	---	---	---	---	---
Dizziness	2 (20.0)	2 (25.0)	1 (14.3)	1 (16.7)	1 (14.3)	2 (22.2)	26 (44.8)	23 (29.5)
Severe	---	---	---	---	---	---	2 (3.4)	---
Drowsiness	2 (20.0)	---	2 (28.6)	---	1 (14.3)	2 (22.2)	7 (12.1)	8 (10.3)
Severe	---	---	---	---	---	---	---	---
Dry Mouth	---	1 (12.5)	2 (28.6)	2 (33.3)	---	1 (11.1)	14 (24.1)	20 (25.6)
Severe	---	---	---	---	---	---	---	---
Fatigue	7 (70.0)	4 (50.0)	5 (71.4)	2 (33.3)	4 (57.1)	4 (44.4)	28 (48.3)	33 (42.3)
Severe	---	---	---	---	---	---	2 (3.4)	---
Headache	8 (80.0)	5 (62.5)	5 (71.4)	4 (66.7)	5 (71.4)	4 (44.4)	29 (50.0)	35 (44.9)
Severe	---	---	---	---	---	---	---	2 (2.6)
Heavy Legs	---	---	---	---	---	---	9 (15.5)	5 (6.4)
Severe	---	---	---	---	---	---	---	---
Impaired Gait/Balance	1 (10.0)	3 (37.5)	---	---	2 (28.6)	1 (11.1)	15 (25.9)	17 (21.8)
Severe	---	---	---	---	---	---	---	---
Impaired Judgement[a]	---	---	---	---	---	---	---	1 (1.3)
Severe	---	---	---	---	---	---	---	---
Increased Irritability	3 (30.0)	---	1 (14.3)	---	---	1 (11.1)	6 (10.3)	5 (6.4)
Severe	---	---	---	---	---	---	1 (1.7)	1 (1.3)
Insomnia	9 (90.0)	2 (25.0)	1 (14.3)	---	1 (14.3)	---	20 (34.5)	22 (28.2)
Severe	---	1 (12.5)	---	---	---	---	1 (1.7)	5 (6.4)
Tight Jaw	3 (30.0)	1 (12.5)	---	2 (33.3)	4 (57.1)	5 (55.6)	37 (63.8)	47 (60.3)
Severe	---	---	---	---	---	1 (11.1)	3 (5.2)	3 (3.8)
Lack of Appetite	2 (20.0)	2 (25.0)	3 (42.9)	---	4 (57.1)	2 (22.2)	29 (50.0)	38 (48.7)
Severe	---	1 (12.5)	---	---	---	---	1 (1.7)	1 (1.3)
Low Mood	2 (20.0)	1 (12.5)	1 (14.3)	---	1 (14.3)	5 (55.6)	12 (20.7)	7 (9.0)

Dose	0 mg (N=10)	25 mg (N=8)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100 mg (N=9)	125 mg (N=58)	Open-label (N=78)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Severe	---	---	---	---	---	---	1 (1.7)	---
Muscle Tension[a]	2 (20.0)	---	5 (71.4)	2 (33.3)	3 (42.9)	4 (44.4)	20 (34.5)	29 (37.2)
Severe	---	---	---	---	---	---	---	---
Nausea	3 (30.0)	2 (25.0)	2 (28.6)	---	2 (28.6)	2 (22.2)	25 (43.1)	29 (37.2)
Severe	---	---	---	---	---	---	4 (6.9)	2 (2.6)
Need More Sleep	3 (30.0)	1 (12.5)	1 (14.3)	2 (33.3)	1 (14.3)	1 (11.1)	5 (8.6)	2 (2.6)
Severe	---	1 (12.5)	---	---	---	---	---	---
Nystagmus	---	---	---	---	1 (14.3)	---	9 (15.5)	10 (12.8)
Severe	---	---	---	---	---	---	---	---
Paresthesia	---	---	1 (14.3)	---	1 (14.3)	---	8 (13.8)	7 (9.0)
Severe	---	---	---	---	---	---	---	---
Perspiration	1 (10.0)	---	2 (28.6)	---	2 (28.6)	3 (33.3)	19 (32.8)	26 (33.3)
Severe	---	---	---	---	---	---	---	---
Restlessness	2 (20.0)	1 (12.5)	4 (57.1)	---	5 (71.4)	3 (33.3)	18 (31.0)	26 (33.3)
Severe	---	---	---	---	---	1 (11.1)	---	---
Ruminations	1 (10.0)	1 (12.5)	2 (28.6)	---	---	2 (22.2)	9 (15.5)	5 (6.4)
Severe	---	---	---	---	---	---	---	---
Sensitivity to Cold	2 (20.0)	1 (12.5)	4 (57.1)	---	4 (57.1)	1 (11.1)	23 (39.7)	22 (28.2)
Severe	---	---	---	---	---	---	---	1 (1.3)
Thirst	1 (10.0)	---	1 (14.3)	1 (16.7)	---	1 (11.1)	17 (29.3)	16 (20.5)
Severe	---	---	---	---	---	---	---	---
Weakness	1 (10.0)	---	---	---	---	2 (22.2)	5 (8.6)	7 (9.0)
Severe	---	---	---	---	---	---	---	---

[a] Diarrhea, impaired judgment, and muscle tension were added based on observations from early studies to reactions list.

Table 54: Prevalence of Spontaneously Reported Reactions During Telephone Contact on Day 1-7 After Experimental Sessions in Sponsor-Supported Phase 2 PTSD Studies of MDMA-Assisted Psychotherapy MP-1, MP-2, MP-4, MP-8, MP-9, MP-12

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Anxiety							
0 mg (N=10)	7 (70.0)	6 (60.0)	5 (50.0)	6 (60.0)	6 (60.0)	6 (60.0)	5 (50.0)
25-40 mg (N=21)	2 (9.5)	7 (33.3)	7 (33.3)	7 (33.3)	7 (33.3)	5 (23.8)	2 (9.5)
75-125 mg (N=74)	23 (31.1)	33 (44.6)	36 (48.6)	25 (33.8)	28 (37.8)	32 (43.2)	19 (25.7)
Open-label (N=78)	19 (24.4)	25 (32.1)	31 (39.7)	28 (35.9)	31 (39.7)	22 (28.2)	14 (17.9)
Diarrhea [a]							
0 mg (N=2)	---	---	---	---	---	---	---
25-40 mg (N=16)	---	---	---	1 (6.3)	1 (6.3)	1 (6.3)	1 (6.3)
75-125 mg (N=50)	1 (2.0)	1 (2.0)	1 (2.0)	1 (2.0)	---	1 (2.0)	---
Open-label (N=62)	---	---	---	---	---	---	---
Difficulty Concentrating							
0 mg (N=10)	3 (30.0)	3 (30.0)	3 (30.0)	3 (30.0)	3 (30.0)	4 (40.0)	1 (10.0)
25-40 mg (N=21)	2 (9.5)	3 (14.3)	2 (9.5)	---	1 (4.8)	---	---
75-125 mg (N=74)	8 (10.8)	7 (9.5)	11 (14.9)	8 (10.8)	10 (13.5)	9 (12.2)	7 (9.5)
Open-label (N=78)	6 (7.7)	6 (7.7)	4 (5.1)	4 (5.1)	3 (3.8)	3 (3.8)	---
Dizziness							
0 mg (N=10)	1 (10.0)	1 (10.0)	1 (10.0)	---	1 (10.0)	---	---
25-40 mg (N=21)	2 (9.5)	1 (4.8)	1 (4.8)	1 (4.8)	---	---	---
75-125 mg (N=74)	6 (8.1)	8 (10.8)	7 (9.5)	6 (8.1)	5 (6.8)	6 (8.1)	3 (4.1)
Open-label (N=78)	4 (5.1)	---	2 (2.6)	2 (2.6)	2 (2.6)	2 (2.6)	1 (1.3)
Drowsiness							
0 mg (N=10)	1 (10.0)	1 (10.0)	1 (10.0)	---	1 (10.0)	---	---
25-40 mg (N=21)	2 (9.5)	1 (4.8)	---	---	---	---	---
75-125 mg (N=74)	1 (1.4)	---	2 (2.7)	1 (1.4)	---	1 (1.4)	1 (1.4)
Open-label (N=78)	4 (5.1)	4 (5.1)	2 (2.6)	1 (1.3)	---	---	---
Dry Mouth							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	---	1 (4.8)	---	---	---	---	---
75-125 mg (N=74)	7 (9.5)	1 (1.4)	4 (5.4)	1 (1.4)	---	1 (1.4)	---
Open-label (N=78)	4 (5.1)	3 (3.8)	---	---	---	1 (1.3)	---
Fatigue							
0 mg (N=10)	6 (60.0)	4 (40.0)	4 (40.0)	6 (60.0)	7 (70.0)	5 (50.0)	4 (40.0)
25-40 mg (N=21)	12 (57.1)	8 (38.1)	6 (28.6)	5 (23.8)	5 (23.8)	5 (23.8)	5 (23.8)
75-125 mg (N=74)	46 (62.2)	34 (45.9)	29 (39.2)	24 (32.4)	23 (31.1)	23 (31.1)	9 (12.2)
Open-label (N=78)	36 (46.2)	38 (48.7)	34 (43.6)	22 (28.2)	20 (25.6)	13 (16.7)	8 (10.3)
Headache							

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
0 mg (N=10)	5 (50.0)	2 (20.0)	1 (10.0)	1 (10.0)	---	---	---
25-40 mg (N=21)	8 (38.1)	3 (14.3)	2 (9.5)	2 (9.5)	2 (9.5)	2 (9.5)	2 (9.5)
75-125 mg (N=74)	19 (25.7)	10 (13.5)	7 (9.5)	9 (12.2)	7 (9.5)	8 (10.8)	3 (4.1)
Open-label (N=78)	23 (29.5)	9 (11.5)	3 (3.8)	4 (5.1)	5 (6.4)	5 (6.4)	---
Heavy Legs							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	---	---	---	---	---	1 (4.8)	---
75-125 mg (N=74)	3 (4.1)	1 (1.4)	---	---	---	1 (1.4)	---
Open-label (N=78)	---	1 (1.3)	2 (2.6)	---	---	---	---
Impaired Gait/Balance							
0 mg (N=10)	---	---	1 (10.0)	---	---	---	---
25-40 mg (N=21)	---	---	---	---	---	---	---
75-125 mg (N=74)	4 (5.4)	---	1 (1.4)	1 (1.4)	1 (1.4)	2 (2.7)	---
Open-label (N=78)	2 (2.6)	---	---	---	---	---	---
Impaired Judgment [a]							
0 mg (N=2)	---	---	---	---	---	---	---
25-40 mg (N=16)	1 (6.3)	1 (6.3)	1 (6.3)	---	---	---	---
75-125 mg (N=50)	---	---	---	---	---	---	---
Open-label (N=62)	---	---	---	---	---	---	---
Increased Irritability							
0 mg (N=10)	2 (20.0)	2 (20.0)	3 (30.0)	2 (20.0)	3 (30.0)	3 (30.0)	---
25-40 mg (N=21)	3 (14.3)	3 (14.3)	3 (14.3)	2 (9.5)	2 (9.5)	1 (4.8)	---
75-125 mg (N=74)	12 (16.2)	13 (17.6)	14 (18.9)	11 (14.9)	11 (14.9)	15 (20.3)	8 (10.8)
Open-label (N=78)	3 (3.8)	4 (5.1)	5 (6.4)	12 (15.4)	6 (7.7)	7 (9.0)	1 (1.3)
Insomnia							
0 mg (N=10)	5 (50.0)	3 (30.0)	5 (50.0)	4 (40.0)	5 (50.0)	7 (70.0)	4 (40.0)
25-40 mg (N=21)	8 (38.1)	8 (38.1)	6 (28.6)	5 (23.8)	4 (19.0)	7 (33.3)	2 (9.5)
75-125 mg (N=74)	37 (50.0)	20 (27.0)	21 (28.4)	16 (21.6)	19 (25.7)	13 (17.6)	8 (10.8)
Open-label (N=78)	19 (24.4)	16 (20.5)	17 (21.8)	15 (19.2)	11 (14.1)	10 (12.8)	6 (7.7)
Tight Jaw							
0 mg (N=10)	2 (20.0)	---	---	---	---	---	---
25-40 mg (N=21)	---	2 (9.5)	1 (4.8)	2 (9.5)	2 (9.5)	1 (4.8)	1 (4.8)
75-125 mg (N=74)	19 (25.7)	11 (14.9)	2 (2.7)	6 (8.1)	5 (6.8)	3 (4.1)	5 (6.8)
Open-label (N=78)	14 (17.9)	6 (7.7)	3 (3.8)	5 (6.4)	3 (3.8)	2 (2.6)	3 (3.8)
Lack of Appetite							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	5 (23.8)	3 (14.3)	3 (14.3)	1 (4.8)	1 (4.8)	1 (4.8)	---
75-125 mg (N=74)	21 (28.4)	17 (23.0)	11 (14.9)	10 (13.5)	7 (9.5)	9 (12.2)	6 (8.1)

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Open-label (N=78)	20 (25.6)	10 (12.8)	8 (10.3)	5 (6.4)	6 (7.7)	3 (3.8)	2 (2.6)
Low Mood							
0 mg (N=10)	2 (20.0)	1 (10.0)	1 (10.0)	4 (40.0)	3 (30.0)	3 (30.0)	1 (10.0)
25-40 mg (N=21)	4 (19.0)	5 (23.8)	5 (23.8)	4 (19.0)	5 (23.8)	4 (19.0)	4 (19.0)
75-125 mg (N=74)	20 (27.0)	25 (33.8)	22 (29.7)	24 (32.4)	20 (27.0)	14 (18.9)	13 (17.6)
Open-label (N=78)	13 (16.7)	17 (21.8)	12 (15.4)	12 (15.4)	13 (16.7)	4 (5.1)	3 (3.8)
Muscle Tension [a]							
0 mg (N=2)	---	---	---	---	---	---	---
25-40 mg (N=16)	4 (25.0)	2 (12.5)	2 (12.5)	2 (12.5)	2 (12.5)	2 (12.5)	2 (12.5)
75-125 mg (N=50)	4 (8.0)	3 (6.0)	---	---	1 (2.0)	2 (4.0)	---
Open-label (N=62)	---	---	---	---	---	---	---
Nausea							
0 mg (N=10)	4 (40.0)	1 (10.0)	1 (10.0)	---	1 (10.0)	---	---
25-40 mg (N=21)	2 (9.5)	3 (14.3)	3 (14.3)	1 (4.8)	1 (4.8)	---	---
75-125 mg (N=74)	16 (21.6)	13 (17.6)	10 (13.5)	6 (8.1)	7 (9.5)	5 (6.8)	4 (5.4)
Open-label (N=78)	12 (15.4)	4 (5.1)	10 (12.8)	6 (7.7)	6 (7.7)	1 (1.3)	1 (1.3)
Need More Sleep							
0 mg (N=10)	3 (30.0)	2 (20.0)	1 (10.0)	2 (20.0)	2 (20.0)	2 (20.0)	2 (20.0)
25-40 mg (N=21)	4 (19.0)	5 (23.8)	3 (14.3)	5 (23.8)	4 (19.0)	5 (23.8)	4 (19.0)
75-125 mg (N=74)	18 (24.3)	25 (33.8)	13 (17.6)	15 (20.3)	9 (12.2)	8 (10.8)	4 (5.4)
Open-label (N=78)	22 (28.2)	20 (25.6)	19 (24.4)	15 (19.2)	15 (19.2)	12 (15.4)	7 (9.0)
Nystagmus							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	---	---	---	---	---	---	---
75-125 mg (N=74)	---	---	---	---	---	---	---
Open-label (N=78)	---	---	---	---	---	---	---
Parasthesia							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	---	---	---	---	---	---	---
75-125 mg (N=74)	1 (1.4)	1 (1.4)	---	1 (1.4)	---	1 (1.4)	1 (1.4)
Open-label (N=78)	---	1 (1.3)	2 (2.6)	1 (1.3)	1 (1.3)	---	---
Perspiration							
0 mg (N=10)	2 (20.0)	---	---	---	---	---	---
25-40 mg (N=21)	1 (4.8)	---	1 (4.8)	---	---	---	---
75-125 mg (N=74)	3 (4.1)	---	1 (1.4)	---	---	---	---
Open-label (N=78)	3 (3.8)	4 (5.1)	1 (1.3)	---	1 (1.3)	1 (1.3)	---
Restlessness							
0 mg (N=10)	---	---	---	---	---	---	---

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
25-40 mg (N=21)	3 (14.3)	1 (4.8)	1 (4.8)	---	2 (9.5)	1 (4.8)	---
75-125 mg (N=74)	8 (10.8)	6 (8.1)	4 (5.4)	6 (8.1)	5 (6.8)	7 (9.5)	3 (4.1)
Open-label (N=78)	1 (1.3)	2 (2.6)	2 (2.6)	3 (3.8)	2 (2.6)	---	---
Ruminations							
0 mg (N=10)	3 (30.0)	1 (10.0)	1 (10.0)	---	---	1 (10.0)	1 (10.0)
25-40 mg (N=21)	2 (9.5)	1 (4.8)	3 (14.3)	3 (14.3)	2 (9.5)	1 (4.8)	1 (4.8)
75-125 mg (N=74)	7 (9.5)	11 (14.9)	12 (16.2)	5 (6.8)	8 (10.8)	10 (13.5)	6 (8.1)
Open-label (N=78)	6 (7.7)	6 (7.7)	7 (9.0)	2 (2.6)	3 (3.8)	2 (2.6)	1 (1.3)
Sensitivity to Cold							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	2 (9.5)	---	---	---	1 (4.8)	1 (4.8)	---
75-125 mg (N=74)	3 (4.1)	3 (4.1)	3 (4.1)	3 (4.1)	1 (1.4)	1 (1.4)	---
Open-label (N=78)	4 (5.1)	1 (1.3)	1 (1.3)	2 (2.6)	1 (1.3)	1 (1.3)	1 (1.3)
Thirst							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	1 (4.8)	---	---	---	---	---	---
75-125 mg (N=74)	5 (6.8)	1 (1.4)	1 (1.4)	1 (1.4)	---	---	---
Open-label (N=78)	---	1 (1.3)	---	---	---	---	---
Weakness							
0 mg (N=10)	---	---	---	---	---	---	---
25-40 mg (N=21)	1 (4.8)	2 (9.5)	---	---	---	---	---
75-125 mg (N=74)	3 (4.1)	7 (9.5)	4 (5.4)	2 (2.7)	4 (5.4)	2 (2.7)	2 (2.7)
Open-label (N=78)	9 (11.5)	1 (1.3)	4 (5.1)	1 (1.3)	---	1 (1.3)	---

[a] Diarrhea, impaired judgment, and muscle tension were added based on observations from early studies to reactions list.

Table 55: Prevalence of Spontaneously Reported Reactions During Open-Label Experimental Sessions and Telephone Contact on Day 1-7 After Experimental Sessions in Sponsor-Supported Phase 1/Phase 2 Study MPVA-1

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Anxiety								
PTSD+ (N=6)	5 (83.3)	3 (50.0)	4 (66.7) +	4 (66.7)	2 (33.3)	4 (66.7)	4 (66.7)	2 (33.3)
CSO (N=6)	4 (66.7)	---	---	3 (50.0)	2 (33.3)	---	1 (16.7)	---
Diarrhea								
PTSD+ (N=6)	---	---	---	---	---	---	---	---
CSO (N=6)	---	1 (16.7)	---	---	---	---	---	---
Difficulty Concentrating								
PTSD+ (N=6)	1 (16.7)	1 (16.7)	---	---	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
CSO (N=6)	1 (16.7)	---	---	1 (16.7)	---	1 (16.7)	1 (16.7)	---
Dizziness								
PTSD+ (N=6)	---	---	---	---	---	---	---	---
CSO (N=6)	2 (33.3)	---	---	---	---	---	---	---
Drowsiness								
PTSD+ (N=6)	---	---	---	---	---	---	---	---
CSO (N=6)	1 (16.7)	---	---	---	---	---	---	---
Dry Mouth								
PTSD+ (N=6)	3 (50.0)	---	---	---	---	---	---	---
CSO (N=6)	---	---	---	---	---	---	---	---
Fatigue								
PTSD+ (N=6)	3 (50.0)	6 (100.0)	1 (16.7)	3 (50.0)	---	2 (33.3)	2 (33.3)	3 (50.0)
CSO (N=6)	3 (50.0)	3 (50.0)	---	---	---	2 (33.3)	---	---
Headache								
PTSD+ (N=6)	5 (83.3)	4 (66.7)	1 (16.7)	2 (33.3)	---	3 (50.0)	1 (16.7)	1 (15.7)
CSO (N=6)	3 (50.0)	5 (83.3)	1 (16.7)	1 (16.7)	---	---	---	---
Impaired Gait/Balance								
PTSD+ (N=6)	1 (16.7)	1 (16.7)	---	---	---	---	---	---
CSO (N=6)	1 (16.7)	2 (33.3)	---	---	---	---	---	---
Increased Irritability								
PTSD+ (N=6)	1 (16.7)	---	---	---	---	1 (16.7)	1 (16.7)	1 (16.7)
CSO (N=6)	---	---	---	---	---	---	---	---
Insomnia								
PTSD+ (N=6)	1 (16.7)	4 (66.7)	1 (16.7)	2 (33.3)	---	2 (33.3)	1 (16.7)	---
CSO (N=6)	---	2 (33.3)	1 (16.7)+	2 (33.3)	1 (16.7)	1 (16.7)	---	1 (16.7)
Tight Jaw								
PTSD+ (N=6)	3 (50.0)	---	---	---	---	---	---	---
CSO (N=6)	4 (66.7)	1 (16.7)	---	1 (16.7)	---	---	---	---

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Lack of Appetite								
PTSD+ (N=6)	5 (83.3)	4 (66.7)	2 (33.3)	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)
CSO (N=6)	5 (83.3)	2 (33.3)	2 (33.3)	1 (16.7)	---	---	---	---
Low Mood								
PTSD+ (N=6)	---	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)
CSO (N=6)	---	---	---	---	---	---	1 (16.7)	---
Muscle Tension								
PTSD+ (N=6)	2 (33.3)	2 (33.3)	1 (16.7)	2 (33.3)	---	---	---	---
CSO (N=6)	2 (33.3)	---	---	---	---	---	1 (16.7)	---
Nausea								
PTSD+ (N=6)	2 (33.3)	3 (50.0)	2 (3.33)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)
CSO (N=6)	1 (16.7)	2 (33.3)	---	---	---	---	---	---
Need More Sleep								
PTSD+ (N=6)	---	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
CSO (N=6)	---	1 (16.7)	1 (16.7)	---	1 (16.7)	---	---	---
Nystagmus								
PTSD+ (N=6)	---	---	---	---	---	---	---	---
CSO (N=6)	---	---	---	---	---	---	---	---
Paraesthesia								
PTSD+ (N=6)	---	---	---	---	---	---	---	---
CSO (N=6)	---	---	---	---	---	---	---	---
Perspiration								
PTSD+ (N=6)	2 (33.3)	---	---	1 (16.7)	---	1 (16.7)	---	---
CSO (N=6)	1 (16.7)	---	---	---	---	---	---	---
Restlessness								
PTSD+ (N=6)	2 (33.3)	---	---	---	---	1 (16.7)	---	---
CSO (N=6)	1 (16.7)	---	---	---	---	---	---	---
Rumination								
PTSD+ (N=6)	---	1 (16.7)	1 (16.7)	---	---	1 (16.7)	---	1 (16.7)
CSO (N=6)	---	---	---	---	---	---	---	---
Sensitivity to Cold								
PTSD+ (N=6)	1 (16.7)	---	---	---	---	---	---	---
CSO (N=6)	2 (33.3)	---	---	---	---	---	---	---
Thirst								
PTSD+ (N=6)	2 (33.3)	---	---	---	---	---	---	---
CSO (N=6)	2 (33.3)	---	---	---	---	---	---	---
Weakness								
PTSD+ (N=6)	---	---	---	---	---	---	---	1 (16.7)

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
CSO (N=6)	---	---	---	---	---	---	---	---

PTSD+ = PTSD diagnosis present, CSO = Concerned Significant Other

In the Phase 1/Phase 2 study MPVA-1, among six dyads consisting of one participant diagnosed with PTSD, along with their concerned significant others (CSO), the most common spontaneously reported reactions during open-label experimental sessions were lack of appetite (83.3% PTSD and 83.3% CSO participants), anxiety (83.3% PTSD and 66.7% CSO participants), headache (83.3% PTSD and 50.0% CSO participants), and tight jaw (50.0% PTSD and 66.7% CSO participants). During the seven days following open-label experimental sessions, at least half of either PTSD or CSO participants reported fatigue (up to 100.0%), headache (up to 83.3%), lack of appetite (up to 83.3%), anxiety (up to 66.7%), insomnia (up to 66.7%), and nausea (up to 50.0%). Fatigue (50.0%) was the most commonly reported reaction that lasted to Day 7 but only among participants with PTSD. Anxiety (33.3%), lack of appetite (33.3%), and nausea (33.3%) were also reported on Day 7, and again, only among participants with PTSD. Overall, few participants reported any reactions later in the week, which suggests most reactions were short-term and self-limiting.

Anxiety Associated with a Life-threatening Illness

Spontaneously reported reactions were collected in a sample of 18 participants in MAPS' Phase 2 study MDA-1 during blinded and open-label sessions with inactive placebo or 125 mg MDMA and a supplemental half-dose. Prevalence of reactions is displayed based on number of participants reporting the reaction at least once (Table 56).

No spontaneously reported reactions during experimental sessions were rated as being severe. The most commonly reported reactions for the active dose groups were tight jaw/jaw clenching (84.6% in 125 mg blinded sessions versus 20.0% in inactive placebo sessions), thirst (84.6% in 125 mg blinded sessions versus 40.0% in inactive placebo sessions), perspiration (69.2% in 125 mg sessions versus none in placebo sessions, dry mouth (69.2% in 125 mg blinded sessions versus 20.0% in inactive placebo sessions), and headache (61.5% in 125 mg MDMA versus 20.0% placebo). The only severely rated reaction for participants in MDA-1 was a single report of Diarrhea recorded during the second day of contact (Day 2) during the 125 mg open-label Stage 2. Owing to the very small sample size, it is difficult to draw firm conclusions concerning frequency of spontaneously reported reactions in this sample.

In the 7-day safety window and comparing blinded session active dose with placebo controls (Table 57), the most commonly reported reactions were fatigue (up to 92.3% in active dose versus 40.0% for inactive placebo), insomnia (up to 46.2% in active dose versus 40.0% in inactive placebo), need more sleep (up to 46.2% in active dose versus 20.0% of inactive placebo), and drowsiness (up to 30.8% in active dose versus 20.0% in inactive placebo). During the seven-day follow-up period after experimental sessions, participants most commonly reported headache (up to 46.2% in active dose versus 40.0% in inactive placebo) and anxiety (up to 30.8% of active dose participants versus 40.0% of inactive placebo). In most cases, number of spontaneously reported reactions declined across days of contact.

In summary, spontaneously reported reactions reported in this small sample of people with anxiety associated with a life-threatening illness receiving 125 mg MDMA were similar to those reported in participants with PTSD. Most of these reactions resolved by or earlier than seven days after drug administration, and were almost entirely mild to moderate, with only a single report of a severe reaction.

Table 56: Prevalence of Spontaneously Reported Reactions During Experimental Sessions in MDA-1

	Number of Participants (%)		
Dose	**0 mg (N=5)**	**125 mg (N=13)**	**Open-label (N=17)**
Anxiety	---	3 (23.1)	2 (11.8)
Diarrhea	---	---	---
Difficulty Concentrating	---	---	---
Dizziness	---	---	---
Drowsiness	---	1 (7.7)	3 (17.6)
Dry Mouth	1 (20.0)	9 (69.2)	8 (47.1)
Fatigue	---	2 (15.4)	5 (29.4)
Headache	1 (20.0)	8 (61.5)	4 (23.5)
Heavy Legs	---	---	---
Impaired Gait/Balance	---	---	1 (5.9)
Impaired Judgment	---	---	---
Increased Irritability	---	---	---
Insomnia	1 (20.0)	2 (15.4)	4 (23.5)
Tight Jaw	1 (20.0)	11 (84.6)	15 (88.2)
Lack of Appetite	---	4 (30.8)	7 (41.2)
Low Mood	---	1 (7.7)	---
Muscle Tension	---	---	---
Nausea	1 (20.0)	3 (23.1)	4 (23.5)
Need More Sleep	---	---	---
Nystagmus	---	1 (7.7)	2 (11.8)
Parasthesia	---	1 (7.7)	1 (5.9)
Perspiration	---	9 (69.2)	7 (41.2)
Restlessness	---	2 (15.4)	2 (11.8)
Ruminations	---	---	---
Sensitivity to Cold	1 (20.0)	2 (15.4)	2 (11.8)
Thirst	2 (40.0)	11 (84.6)	9 (52.9)
Weakness	---	---	1 (5.9)

[1] No severe reactions reported.

Table 57: Prevalence of Spontaneously Reported Reactions During Telephone Contact on Day 1-7 After Experimental Sessions in MDA-1

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Anxiety							
0 mg (N=5)	---	1 (20.0)	2 (40.0)	---	1 (20.0)	---	1 (20.0)
125 mg (N=13)	4 (30.8)	3 (23.1)	4 (30.8)	4 (30.8)	1 (7.7)	2 (15.4)	4 (30.8)
Open-label (N=17)	1 (5.9)	5 (29.4)	5 (29.4)	5 (29.4)	4 (23.5)	5 (29.4)	1 (5.9)
Diarrhea							
0 mg (N=5)	---	---	---	---	---	1 (20.0)	---
125 mg (N=13)	---	---	---	---	---	---	1 (7.7)
Open-label (N=17)	---	1 (5.9)[a]	---	---	1 (5.9)	---	---
Difficulty Concentrating							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	2 (15.4)	---	---	---	---
Open-label (N=17)	2 (11.8)	3 (17.6)	3 (17.6)	---	---	---	---
Dizziness							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	1 (5.9)	---	---	---	---	---	---
Drowsiness							
0 mg (N=5)	---	---	1 (20.0)	---	---	---	---
125 mg (N=13)	4 (30.8)	---	1 (7.7)	---	---	---	---
Open-label (N=17)	1 (5.9)	2 (11.8)	1 (5.9)	1 (5.9)	---	---	---
Dry Mouth							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	2 (15.4)	1 (7.7)	1 (7.7)	---	---	---	---
Open-label (N=17)	3 (17.6)	2 (11.8)	---	---	---	---	---
Fatigue							
0 mg (N=5)	---	2 (40.0)	1 (20.0)	2 (40.0)	---	---	---
125 mg (N=13)	6 (46.2)	9 (69.2)	12 (92.3)	8 (61.5)	8 (61.5)	6 (46.2)	5 (38.5)
Open-label (N=17)	7 (41.2)	13 (76.5)	10 (58.8)	5 (29.4)	7 (41.2)	2 (11.8)	---
Headache							
0 mg (N=5)	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)	---	---	---
125 mg (N=13)	6 (46.2)	4 (30.8)	2 (15.4)	2 (15.4)	---	---	---
Open-label (N=17)	7 (41.2)	5 (29.4)	2 (11.8)	2 (11.8)	2 (11.8)	1 (5.9)	---
Heavy Legs							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Impaired Gait/Balance							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	---	---	1 (7.7)	1 (7.7)	---
Open-label (N=17)	1 (5.9)	---	---	---	---	---	---
Impaired Judgment							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Increased Irritability							
0 mg (N=5)	---	---	---	---	1 (20.0)	1 (20.0)	1 (20.0)
125 mg (N=13)	---	---	---	---	1 (7.7)	2 (15.4)	1 (7.7)
Open-label (N=17)	---	---	---	---	---	---	2 (11.8)
Insomnia							
0 mg (N=5)	---	---	2 (40.0)	1 (20.0)	---	---	---
125 mg (N=13)	6 (46.2)	2 (15.4)	2 (15.4)	---	---	---	---
Open-label (N=17)	3 (17.6)	4 (23.5)	1 (5.9)	2 (11.8)	---	2 (11.8)	3 (17.6)
Tight Jaw							
0 mg (N=5)	1 (20.0)	---	---	---	---	---	---
125 mg (N=13)	7 (53.8)	4 (30.8)	3 (23.1)	1 (7.7)	---	---	---
Open-label (N=17)	9 (52.9)	8 (47.1)	4 (23.5)	3 (17.6)	2 (11.8)	1 (5.9)	1 (5.9)
Lack of Appetite							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	2 (15.4)	1 (7.7)	---	1 (7.7)	---	---	---
Open-label (N=17)	---	---	1 (5.9)	---	---	---	---
Low Mood							
0 mg (N=5)	---	1 (20.0)	1 (20.0)	1 (20.0)	3 (60.0)	1 (20.0)	2 (40.0)
125 mg (N=13)	3 (23.1)	5 (38.5)	5 (38.5)	1 (7.7)	3 (23.1)	2 (15.4)	2 (15.4)
Open-label (N=17)	1 (5.9)	5 (29.4)	7 (41.2)	1 (5.9)	5 (29.4)	3 (17.6)	1 (5.9)
Muscle Tension							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	1 (7.7)	1 (7.7)	1 (7.7)	1 (7.7)	---	---	---
Open-label (N=17)	1 (5.9)	---	---	2 (11.8)	---	---	---
Nausea							
0 mg (N=5)	1 (20.0)	1 (20.0)	1 (20.0)	1 (20.0)	---	---	---
125 mg (N=13)	2 (15.4)	4 (30.8)	4 (30.8)	2 (15.4)	1 (7.7)	1 (7.7)	1 (7.7)
Open-label (N=17)	2 (11.8)	---	---	---	---	---	---
Need More Sleep							
0 mg (N=5)	1 (20.0)	1 (20.0)	---	---	---	---	1 (20.0)

Post-drug	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
125 mg (N=13)	5 (38.5)	6 (46.2)	6 (46.2)	2 (15.4)	1 (7.7)	2 (15.4)	---
Open-label (N=17)	1 (5.9)	7 (41.2)	5 (29.4)	2 (11.8)	2 (11.8)	1 (5.9)	1 (5.9)
Nystagmus							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Parasthesia							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Perspiration							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	---	---
Open-label (N=17)	1 (5.9)	---	---	---	---	---	---
Restlessness							
0 mg (N=5)	---	---	1 (20.0)	---	1 (20.0)	1 (20.0)	1 (20.0)
125 mg (N=13)	1 (7.7)	---	---	---	1 (7.7)	---	---
Open-label (N=17)	---	---	---	1 (5.9)	1 (5.9)	---	---
Ruminations							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	---	---	---	---	1 (7.7)	---
Open-label (N=17)	---	---	2 (11.8)	---	---	1 (5.9)	1 (5.9)
Sensitivity to Cold							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	---	1 (7.7)	---	---	---	---	---
Open-label (N=17)	---	---	---	---	---	---	---
Thirst							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	2 (15.4)	---	---	---	---	---	---
Open-label (N=17)	2 (11.8)	1 (5.9)	1 (5.9)	---	---	---	--
Weakness							
0 mg (N=5)	---	---	---	---	---	---	---
125 mg (N=13)	1 (7.7)	---	1 (7.7)	---	---	---	---
Open-label (N=17)	---	1 (5.9)	---	---	---	---	---

[a] One severe report of diarrhea on Day 2 contact. All other reactions were mild or moderate.

Social Anxiety in Autistic Adults

Spontaneously reported reactions were collected in a sample of 12 individuals within MAPS' study MAA-1 (Table 58). Participants in this study received inactive placebo or ascending doses, with the first session being either 75 or 100 mg MDMA and the second session being 100 or 125 mg MDMA or 100 and 125 mg; participants in Stage 2 all received 75 mg in Session 1 and 125 mg in Session 2. No supplemental dose was administered in this study. Prevalence of reactions is displayed based on number of participants reporting the reaction at least once.

None of the spontaneously reported reactions during experimental sessions were rated as severe. Most commonly reported were anxiety (75.0% of those receiving 75-125 mg in blinded sessions and 25.0% of those receiving 75-125 mg in open-label sessions versus 25.0% in inactive placebo sessions), lack of appetite (37.5% of those receiving 75-125 mg in blinded sessions and 75.0% of those receiving 75-125 mg in open-label sessions versus 25% in inactive placebo sessions), and difficulty concentrating (62.5% in 75-125 mg blinded sessions, 50% in 75-125 mg open-label sessions versus 25% inactive placebo). Additionally, at least 50% of participants in either the 75-125 mg blinded sessions or 75-125 mg open-label sessions reported fatigue (vs. 25.0% inactive placebo), headache (vs. 25.0% inactive placebo), muscle tension (vs. 25.0% inactive placebo), perspiration (vs. 25.0% inactive placebo), rumination (vs. 0% in inactive placebo), and sensitivity to cold (0% inactive placebo). The only severe spontaneously reported reaction in this sample was a single report of headache in a participant in the 75-125 mg group on the first day of contact.

Most commonly reported spontaneously reported reactions among participants on the autism spectrum with social anxiety during the seven days after experimental sessions was fatigue (up to 75.0% in the 75-125 mg groups versus 50.0% in the inactive placebo group) (Table 58). Low mood (up to 50.0% in the 75-125 mg groups vs. 50.0% in the inactive placebo group), headache (up to 37.5% in the 75-125 mg groups vs. 25.0% in the inactive placebo group), difficulty concentrating (up to 37.5% in the 75-125 mg blinded group vs. 0% in the inactive placebo group), and lack of appetite (up to 37.5% in the 75-125 mg blinded group vs. 0% in the inactive placebo group) were also reported. This sample reported experiencing fewer reactions during the seven-day period than participants with PTSD; there were no reports of diarrhea, impaired gait, or nausea. However, the sample consisted of 12 participants, and a slightly lower dose of 75 mg was used in blinded and open-label sessions.

Spontaneously reported reactions after 75-125 mg MDMA in autistic adult participants with social anxiety were also mild to moderate and transient, which was similar to other studies conducted for treatment of different indications. In summary, commonly reported acute and sub-acute reactions to MDMA are generally well-tolerated and are rarely reported after the 24-hour period beyond drug administration. Reports of reactions grow increasingly rare after the third day of contact.

Table 58: Prevalence of Spontaneously Reported Reactions During Experimental Sessions and Telephone Contact on Day 1-7 After Experimental Sessions in Sponsor-Supported Phase 2 Study MAA-1

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Anxiety								
0 mg (N=4)	1 (25.0)	---	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	6 (75.0)	1 (12.5)	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	---	---	---	---	---	---	---
Diarrhea								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	---	---	---	---	---	---	---
Difficulty Concentrating								
0 mg (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	5 (62.5)	1 (12.5)	3 (37.5)	1 (12.5)	---	---	1 (12.5)	---
Open-label (N=4)	2 (50.0)	---	---	---	---	---	---	---
Dizziness								
0 mg (N=4)	1 (25.0)	---	---	---	---	---	1 (25.0)	1 (25.0)
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Drowsiness								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	1 (12.5)	---
Open-label (N=4)	1 (25.0)	---	---	---	---	---	---	---
Dry Mouth								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Fatigue								
0 mg (N=4)	1 (25.0)	---	2 (50.0)	---	---	---	---	---
75-125 mg (N=8)	4 (50.0)	3 (37.5)	3 (37.5)	1 (12.5)	---	---	1 (12.5)	---
Open-label (N=4)	---	2 (50.0)	3 (75.0)	---	---	1 (25.0)	1 (25.0)	1 (25.0)
Headache								
0 mg (N=4)	1 (25.0)	1 (25.0)	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	4 (50.0)	3 (37.5)[a]	2 (25.0)	---	---	3 (37.5)	2 (25.0)	1 (12.5)
Open-label (N=4)	---	1 (25.0)	1 (25.0)	---	---	1 (25.0)	---	---
Heavy Legs								

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Impaired Gait/Balance								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Impaired Judgment								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Increased Irritability								
0 mg (N=4)	---	---	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	1 (12.5)	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Insomnia								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	1 (12.5)	1 (12.5)	1 (12.5)	---	1 (12.5)	1 (12.5)	---
Open-label (N=4)	---	1 (25.0)	1 (25.0)	---	---	---	---	---
Tight Jaw								
0 mg (N=4)	---	---	1 (25.0)	---	---	---	---	1 (25.0)
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	---	1 (25.0)	---	---	---	---	---	---
Lack of Appetite								
0 mg (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	3 (37.5)	3 (37.5)	1 (12.5)	---	---	---	---	---
Open-label (N=4)	3 (75.0)	---	---	---	---	---	---	---
Low Mood								
0 mg (N=4)	---	---	1 (25.0)	---	---	---	2 (50.0)	1 (25.0)
75-125 mg (N=8)	2 (25.0)	2 (25.0)	4 (50.0)	---	---	1 (12.5)	1 (12.5)	1 (12.5)
Open-label (N=4)	---	1 (25.0)	1 (25.0)	---	---	---	---	1 (25.0)
Muscle Tension								
0 mg (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	3 (37.5)	---	---	---	---	---	---	---
Open-label (N=4)	2 (50.0)	---	---	---	---	1 (25.0)	---	---

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Nausea								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Need More Sleep								
0 mg (N=4)	---	1 (25.0)	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	2 (25.0)	---	1 (12.5)	---	---	---	---
Open-label (N=4)	---	3 (75.0)	2 (50.0)	---	---	---	---	---
Nystagmus								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Parasthesia								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	---	1 (12.5)	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	1 (25.0)	---	---	---	---	---	---
Perspiration								
0 mg (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	2 (50.0)	---	---	---	---	---	---	---
Restlessness								
0 mg (N=4)	1 (25.0)	---	---	---	---	---	---	---
75-125 mg (N=8)	3 (37.5)	---	---	---	---	---	---	---
Open-label (N=4)	1 (25.0)	---	1 (25.0)	---	---	---	---	---
Ruminations								
0 mg (N=4)	---	---	---	---	---	---	1 (25.0)	---
75-125 mg (N=8)	1 (12.5)	---	---	---	---	---	---	---
Open-label (N=4)	2 (50.0)	---	---	---	---	---	---	---
Sensitivity to Cold								
0 mg (N=4)	---	---	---	---	---	---	---	1 (25.0)
75-125 mg (N=8)	4 (50.0)	---	---	---	---	---	---	---
Open-label (N=4)	---	---	---	---	---	---	---	---
Thirst								
0 mg (N=4)	---	---	---	---	---	---	---	---
75-125 mg (N=8)	2 (25.0)	1 (12.5)	---	---	---	---	---	---

Post-drug	Day 0 N (%)	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)
Open-label (N=4)	---	---	---	---	---	---	---	---
Weakness								
0 mg (N=4)	1 (25.0)	---	1 (25.0)	---	---	---	---	---
75-125 mg (N=8)	1 (12.5)	1 (12.5)	1 (12.5)	---	---	---	---	---
Open-label (N=4)	---	---	1 (25.0)	---	---	---	---	---

[a] One severe reaction.

5.3.9.2 Adverse Events

Frequency of AEs among participants with PTSD treated with MDMA at any dose across nine MAPS-sponsored studies conducted under U.S. IND are summarized in Tables 59-62. Adverse events were collected throughout the treatment period, and medically important AEs were collected at Long-term Follow-up (12 months or more). Based on the elimination half-life of 7 to 9 hours for active doses of MDMA, it is difficult to judge relationships of AEs reported during/after the 7-day safety window as they may also be related to the therapeutic process or background events. No IND safety reports have been reportable to date for MDMA in MAPS-sponsored studies.

Most AEs reported across dose groups within studies of people with PTSD fall within the MedDRA System Organ class of psychiatric disorders, followed by musculoskeletal and connective tissue disorders, general disorders, gastrointestinal disorders, nervous system disorders, infections and infestations, and eye disorders. More specifically, participants administered any active dose of MDMA commonly reported irritability (up to 5.4%), headache (up to 9.5%), visual impairment (up to 6.8%), vomiting (up to 6.8%), and nausea (up to 5.4%) during experimental sessions. Overall, among those dosed with active MDMA, the frequency of any given reported AE was less than 10%. Participants in the 0 mg blinded group did not report these specific events, which suggests MDMA could have induced these AE's. Further study however is needed to elucidate relationships between MDMA and specific AE's that might be expected during drug administration.

Commonly reported AE's across blinded 0 mg, 25-40 mg, 75-100 mg, and open-label 100-150 mg participants included anxiety, depressed mood, and fatigue. The prevalence of these events across groups, which included blinded 0 mg participants, suggest that these events likely occurred in response to other factors associated with study participation, such as participants' medical histories and/or psychotherapy, and were independent of MDMA drug administration. For example, a higher proportion of blinded 0 mg participants reported anxiety (20%) and fatigue (20%) compared to any dosed groups; and nearly the same proportion of blinded 0 mg participants (10.0%) reported having depressed mood compared to blinded 75-125 mg participants (10.8%). Overall, in participants with PTSD, the majority of AE's were likely unrelated to drug administration and/ or were not reported at 12-month follow-up.

Since MDMA is administered as an adjunct to psychotherapy, judging relationships to study drug is a known challenge for this combined therapy. In the context of complex medical histories associated with the PTSD diagnosis, somatic symptoms may wax and wane independent of treatment. In addition, it is known that processing trauma during psychotherapy for PTSD, with or without concomitant pharmacological treatment, can temporarily increase symptoms as an expected aspect of the therapeutic process. This was demonstrated by the high incidence of spontaneously reported reactions and AEs in the placebo group. Multiple severe AEs were rarely reported by the same subject.

It is noteworthy there was one, moderately severe, expected cardiac SAR, that was deemed serious because the participant was monitored overnight due to increased ventricular extrasystoles. No severe cardiac, renal and urinary, or vascular disorders were reported, and they were also among the least frequently reported types of AEs after any MDMA dose. In contrast, epidemiologic studies have reported incidents of cardiovascular toxicity, hyperthermia, ARF, hyponatremia, and neurotoxicity, as described in Section 4.5 Serious Reports, Mortality, and Morbidity in Animals and Epidemiological Settings and in Table 2. AEs in these body systems were less frequently reported in sponsored-supported studies, compared to epidemiologic studies, which suggests treatment under controlled clinical settings with proper medical screening can prevent occurrence of severe cardiac, renal and urinary, and vascular events.

Table 59: Adverse Events by Body System Organ Class (MedDRA 17.1) among Participants with PTSD in Sponsor-Supported Phase 2 Studies of MDMA-Assisted Psychotherapy

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
Subjects per Dose Group		10	21	74	74	90
Participants who reported an AE		9	11	55	53	8
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Cardiac disorders						
	Palpitations					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Sinus tachycardia					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Ventricular extrasystoles					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
Ear and labyrinth disorders						

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Tinnitus					
	Any	---	1 (4.8)	1 (1.4)	---	---
	Severe	---	---	---	---	---
Endocrine disorders						
	Hypothyroidism					
	Any	---	1 (4.8)	1 (1.4)	---	---
	Severe	---	---	---	---	---
Eye disorders						
	Dry Eye					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Vision blurred					
	Any	---	---	1 (1.4)	1 (1.4)	---
	Severe	---	---	---	---	---
	Visual impairment					
	Any	---	---	5 (6.8)	1 (1.4)	---
	Severe	---	---	---	---	---
	Vitreous floaters					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
Gastrointestinal disorders						
	Abdominal pain					
	Any	---	---	2 (2.7)	2 (2.7)	---
	Severe	---	---	---	1 (1.4)	---
	Abdominal pain, upper					
	Any	1 (10.0)	---	---	---	---
	Severe	--	---	---	---	---
	Constipation					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Diarrhea					
	Any	---	1 (4.8)	4 (5.4)	2 (2.7)	---
	Severe	---	---	---	---	---
	Dyspepsia					

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Any	---	---	1 (1.4)	1 (1.4)	---
	Severe	---	---	---	---	---
	Gastric Ulcer					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Intestinal obstruction					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	1 (1.4)	---	---
	Irritable Bowel Syndrome					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Nausea					
	Any	---	---	4 (5.4)	1 (1.4)	---
	Severe	---	---	---	---	---
	Oropharyngeal blistering					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Vomiting					
	Any	---	---	5 (6.8)	1 (1.4)	---
	Severe	---	---	---	---	---
General disorders and administrative site conditions						
	Asthenia					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Chills					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Cyst					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Fatigue					
	Any	2 (20.0)	4 (19.0)	6 (8.1)	4 (5.4)	---
	Severe	---	---	---	---	---
	Facial pain					

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Any	1 (10.0)	---	---	---	---
	Severe	---	---	---	---	---
	Feeling abnormal					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Feeling hot					
	Any	---	---	2 (2.7)	---	---
	Severe	---	---	---	---	---
	Influenza-like illness					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Malaise					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Pain					
	Any	1 (10.0)	2 (9.5)	2 (2.7)	2 (2.7)	---
	Severe	---	1 (4.8)	---	---	---
	Pyrexia					
	Any	---	1 (4.8)	2 (2.7)	2 (2.7)	---
	Severe	---	---	---	---	---
Infections and infestations						
	Angina tonsils					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Appendicitis					
	Any	---	---	---	---	1 (1.1)
	Severe	---	---	---	---	1 (1.1)
	Hordeolum					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
	Influenza					
	Any	---	2 (9.5)	2 (2.7)	---	---
	Severe	---	---	---	---	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Laryngitis					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Otitis Media					
	Any	1 (10.0)	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
	Pharyngitis					
	Any	1 (10.0)	---	---	---	---
	Severe	---	---	---	---	---
	Pharyngitis, streptococcal					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Pneumonia					
	Any	---	---	1 (1.4)	2 (2.7)	---
	Severe	---	---	---	---	---
	Pneumonia, chlamydia					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Sinusitis					
	Any	---	1 (4.8)	2 (2.7)	---	---
	Severe	---	---	1 (1.4)	---	---
	Tinea pedis					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Tooth abscess					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
	Upper respiratory tract infection					
	Any	1 (10.0)	---	1 (1.4)	4 (5.4)	---
	Severe	---	---	---	---	---
	Urinary tract infection					
	Any	---	---	1 (1.4)	2 (2.7)	---
	Severe	---	---	---	---	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Vaginal infection					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
Immune system disorders						
	Hypersensitivity					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
Injury, poisoning, procedural complications						
	Concussion					
	Any	---	---	---	1 (1.4)	1 (1.1)
	Severe	---	---	---	1 (1.4)	---
	Contusion					
	Any	---	---	2 (2.7)	---	---
	Severe	---	---	---	---	---
	Exposure to violent event					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	1 (1.4)	---
	Incorrect dose administered					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Joint dislocation					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Ligament sprain					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
	Limb injury					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Lower limb fracture					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	1 (1.4)	---	---
	Post-concussion syndrome					
	Any	---	---	---	---	1 (1.1)

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Severe	---	---	---	---	---
	Road traffic accident					
	Any	---	---	---	---	1 (1.1)
	Severe	---	---	---	---	---
	Skeletal injury					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Skin abrasion					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
Investigations						
	Red blood cell sedimentation rate increased					
	Any	---	---	---	---	1 (1.1)
	Severe	---	---	---	---	---
Metabolism and nutrition disorders						
	Anorexia					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Decreased appetite					
	Any	---	---	1 (1.4)	1 (1.4)	---
	Severe	---	---	---	---	---
	Iron deficiency anemia					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Vitamin D deficiency					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
Musculoskeletal and connective tissue disorders						
	Arthralgia					
	Any	1 (10.0)	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Back pain					
	Any	1 (10.0)	---	2 (2.7)	2 (2.7)	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Severe	---	---	---	---	---
	Clavicle fracture					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Joint stiffness					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Muscle spasms					
	Any	1 (10.0)	---	2 (2.7)	1 (1.4)	---
	Severe	---	---	---	---	---
	Muscle strain					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Muscle tightness					
	Any	1 (10.0)	---	7 (9.5)	2 (2.7)	---
	Severe	---	---	---	---	---
	Muscle twitching					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Musculoskeletal chest pain					
	Any	1 (10.0)	---	---	---	---
	Severe	1 (10.0)	---	---	---	---
	Musculoskeletal pain					
	Any	---	---	2 (2.7)	1 (1.4)	---
	Severe	---	---	---	---	---
	Musculoskeletal stiffness					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Myalgia					
	Any	---	---	---	5 (6.8)	---
	Severe	---	---	---	---	---
	Neck pain					
	Any	1 (10.0)	---	---	2 (2.7)	---
	Severe	---	---	---	---	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Pain in extremity					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
Neoplasms benign, malignant and unspecified						
	Breast cancer stage 1					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	1 (1.4)	---
	Metastases to central nervous system					
	Any	---	---	---	---	1 (1.1)
	Severe	---	---	---	---	1 (1.1)
Nervous system disorders						
	Burning sensation					
	Any	1 (10.0)	---	1 (1.4)	1 (1.4)	---
	Severe	---	---	---	---	---
	Dizziness					
	Any	---	---	3 (14.3)	2 (2.7)	---
	Severe	---	---	---	---	---
	Headache					
	Any	---	2 (9.5)	5 (6.8)	2 (2.7)	---
	Severe	---	1 (4.8)	---	---	---
	Hypoaesthesia facial					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Hypersomnia					
	Any	---	1 (4.8)	---	3 (4.1)	---
	Severe	---	---	---	---	---
	Migraine					
	Any	---	1 (4.8)	---	1 (1.4)	---
	Severe	---	1 (4.8)	---	---	---
	Myoclonus					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Paresthesia					
	Any	---	---	1 (1.4)	---	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Severe	---	---	--	---	---
	Sciatica					
	Any	1 (10.0)	---	---	---	---
	Severe	1 (10.0)	---	---	---	---
	Syncope					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Tension headache					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Tremor					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
Psychiatric disorders						
	Agitation					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Anger					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	1 (1.4)	---
	Anxiety					
	Any	2 (20.0)	2 (14.3)	13 (17.6) (2)	10 (13.5)	3 (3.3)
	Severe	---	---	1 (1.4)	---	1 (1.1)
	Bruxism					
	Any	---	---	2 (2.7)	1 (1.4)	---
	Severe	---	---	---	---	---
	Depressed mood					
	Any	1 (10.0)	2 (14.3)	8 (10.8)	2 (2.7)	---
	Severe	---	---	2 (2.7)	---	---
	Depression					
	Any	---	---	1 (1.4)	---	2 (2.2)
	Severe	---	---	---	---	1 (1.1)
	Derealization					

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Dissociation					
	Any	1 (10.0)	1 (4.8)	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Disturbance in attention					
	Any	---	---	3 (4.1)	---	---
	Severe	---	---	---	---	---
	Emotional distress					
	Any	1 (10.0)	1 (4.8)	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Flashback					
	Any	1 (10.0)	---	1 (1.4)	---	---
	Severe	1 (10.0)	---	---	---	---
	Hypnagogic hallucination					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Hypnopompic hallucination					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Insomnia					
	Any	1 (10.0)	1 (4.8)	2 (2.7)	4 (5.4)	---
	Severe	---	1 (4.8)	---	---	---
	Intentional self-injury					
	Any	1 (10.0)	1 (4.8)	---	1 (1.4)	1 (1.1)
	Severe	---	---	---	---	---
	Irritability					
	Any	---	---	4 (5.4)	1 (1.4)	---
	Severe	---	---	---	---	---
	Major depression					
	Any	---	---	1 (1.4)	---	1 (1.1)
	Severe	---	---	1 (1.4)	---	---
	Memory impairment					
	Any	1 (10.0)	---	---	---	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Severe	---	---	---	---	---
	Negative thoughts					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
	Obsessive rumination					
	Any	---	---	2 (2.7)	1 (1.4)	---
	Severe	---	---	1 (1.4)	---	---
	Panic attack					
	Any	---	---	3 (4.1)	---	1 (1.1)
	Severe	---	---	2 (2.7)	---	---
	Post-traumatic stress disorder					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Restlessness					
	Any	---	---	2 (2.7)	---	---
	Severe	---	---	---	---	---
	Somatoform disorder					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Somnolence					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Suicidal ideation					
	Any	---	1 (4.8)	1 (1.4)	2 (2.7)	2 (2.2)
	Severe	---	1 (4.8)	1 (1.4)	---	1 (1.1)
	Tension					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Tic					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Time perception altered					
	Any	---	1 (4.8)	---	---	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Severe	---	---	---	---	---
	Trichotillomania					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
Renal and urinary disorders						
	Dysuria					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Nocturia					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
Reproductive disorders						
	Ovarian Cyst					
	Any	---	---	1 (1.4)	---	1 (1.1)
	Severe	---	---	---	---	---
	Ovarian cyst ruptured					
	Any	---	---	---	---	1 (1.1)
	Severe	---	---	---	---	1 (1.1)
Respiratory, thoracic and mediastinal disorders						
	Asthma					
	Any	---	---	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Cough					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
	Dyspnea					
	Any	---	---	2 (2.7))	---	---
	Severe	---	---	---	---	---
	Nasal congestion					
	Any	---	1 (4.8)	---	1 (1.4)	---
	Severe	---	---	---	---	---
	Oropharyngeal pain					
	Any	---	---	1 (1.4)	2 (2.7)	---
	Severe	---	---	---	---	---

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Sinus headache					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Throat tightness					
	Any	1 (10.0)	---	---	---	---
	Severe	---	---	---	---	---
Skin and subcutaneous tissue disorders						
	Dermatitis					
	Any	1 (10.0)	---	---	---	---
	Severe	---	---	---	---	---
	Petechiae					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Pruritis					
	Any	1 (10.0)	---	---	2 (2.7)	---
	Severe	---	---	---	---	---
	Pseudofolliculitis barbae					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Psoriasis					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Urticaria					
	Any	---	1 (4.8)	---	---	---
	Severe	---	---	---	---	---
Surgical and medical procedures						
	Foot operation					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
Vascular disorders						
	Hypertension					
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
	Deep vein thrombosis					

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 25-40 mg	Blinded 75-125 mg	Open-label 100-150 mg	12-month Follow-up
	Any	---	---	1 (1.4)	---	---
	Severe	---	---	---	---	---
Not codable						
	Auto accident, no injury					
	Any	1 (10.0)	---	---	---	---
	Severe	---	---	---	---	---

Among related AEs reported during and after drug administration, somatic symptoms were more frequently experienced in active dose participants, such as pain associated with body tension, muscle tightness, musculoskeletal pain in the shoulder, back pain, and myalgia. As previously discussed in Section 5.3.9.2 Adverse Events, it is difficult to judge relationship between study drug and conditions associated with medical history diagnoses. Pain and somatic symptoms can be directly related to traumatic events, such as physical or sexual assault, a motor vehicle accident, or combat [704]. A meta-analytic review and several large studies have found a robust association between PTSD and somatic symptoms, suggesting that PTSD itself may be a contributing factor beyond combat exposure, sexual, or physical abuse that led to the PTSD [705-708].

Although MDMA is not a classic hallucinogen, as classified by chemical structure and mechanism of action, data from sponsor-supported studies suggest MDMA was associated with mild psychedelic effects, such as hypnagogic and hypnopompic hallucinations and visual distortions in some individuals. Hallucinogenic subjective effects were not actively assessed during therapy sessions, as was done in Phase 1 studies of healthy volunteers [8, 11, 12, 628]. Any unsolicited reports of hallucinogenic effects were collected as AEs in sponsor-supported studies.

Table 60: Adverse Events by System Organ Class (MedDRA 17.1) in Sponsor-Supported Phase 1/Phase 2 Study MPVA-1 of MDMA-Assisted Psychotherapy for Dyads of PTSD Participant with Concerned Significant Other

SOC	Adverse Event Preferred Term[a]	PTSD+ Open-label (75-100 mg MDMA)	PTSD+ 6-month Follow-up	CSO Open-label (75-100 mg MDMA)	CSO 6-month Follow-up
Participants per group		6	6	6	6
Participants who reported an AE		6	2	6	2
		N (%)	N (%)	N (%)	N (%)
Ear and labyrinth disorders					
	Tinnitus	1 (16.7)			
Eye disorders					
	Visual impairment			1 (16.7)	
Endocrine disorders					
	Hypothyroidism		1 (16.7)		
Gastrointestinal disorders					
	Nausea	2 (33.3)			
	Vomiting			1 (16.7)	
General disorders and admin site conditions					
	Asthenia	1 (16.7)			
	Fatigue	2 (33.3)			
Infections and infestations					
	Acute sinusitis	1 (16.7)			
	Nasopharyngitis	1 (16.7)			
	Upper respiratory tract infection	2 (33.3)		1 (16.7)	
	Tooth infection		1 (16.7)		
	Urethritis		1 (16.7)		
Injury, poisoning and procedural complications					
	Arthropod bite			1 (16.7)	
Metabolism and nutrition disorders					
	Decreased appetite	2 (33.3)			
Nervous system disorders					
	Disturbance in attention	1 (16.7)		1 (16.7)	
	Dizziness			1 (16.7)	
	Paresthesia			1 (16.7)	
	Tremor	1 (16.7)			
Pregnancy, puerperium and perinatal conditions					
	Abortion, spontaneous				1 (16.7)
Psychiatric disorders					
	Anxiety	1 (16.7)		1 (16.7)	1 (16.7)
	Insomnia			1 (16.7)	
	Tic	1 (16.7)			
Renal and urinary disorders					
	Dysuria	1 (16.7)			
Respiratory disorders					
	Nasal congestion			1 (16.7)	
	Oropharyngeal pain			1 (16.7)	
	Rhinorrhoea			1 (16.7)	
	Dyspnoea			1 (16.7)	
Skin and subcutaneous tissue disorders					
	Erythema	1 (16.7)			
	Pruritis			1 (16.7)	
	Rash			1 (16.7)	

[1] No severe AEs.

In MPVA-1, a total of six dyads (N=12), each consisting of one participant with PTSD and a concerned significant other (CSO), received MDMA-assisted psychotherapy with an initial dose of 75 to100 mg, and a supplemental dose of 37.5-50 mg dose. All 12 participants reported an AE during an experimental session. Only three AEs were shared between PTSD participants and CSOs: upper respiratory tract infection (33.3% in PTSD participants vs. 16.7% CSOs), disturbance in attention (16.7% in PTSD participants vs. 16.7% CSOs), and anxiety (16.7% PTSD participants vs. 16.7% CSOs). Most frequently reported AEs that were unique to PTSD participants included nausea (33.3%), fatigue (33.3%), and decreased appetite (33.3%). At 6-month follow-up, a total of two participants with PTSD reported three AEs and two CSOs reported two AEs. No AEs reported at long-term follow up overlapped between PTSD participants and their CSOs, and AEs were likely unrelated to drug administration. Further investigation is needed to determine relationships between drug administration and AEs in participants with and without PTSD to elucidate potential AEs specifically related to PTSD.

Table 61: Treatment-Emergent Adverse Events by System Organ Class (MedDRA 17.1) in Sponsor-Supported Phase 2 Open-Label Studies MP16 and MP17 from Date of First Dose to Study Termination

SOC	Adverse Event Preferred Term	Open-label 80-120 mg
Participants		28
Participants who reported an AE		28
		N (%)
Cardiac disorders		
	Palpitations	3 (10.7)
Ear and labyrinth disorders		
	Ear discomfort	1 (3.6)
	Ocular discomfort	1 (3.6)
	Photophobia	1 (3.6)
	Vision blurred	1 (3.6)
	Visual impairment	1 (3.6)
Gastrointestinal disorders		
	Abdominal discomfort	3 (10.7)
	Anal fissure	1 (3.6)
	Aphthous ulcer	1 (3.6)
	Diarrhoea	1 (3.6)
	Dry mouth	2 (7.1)
	Eructation	1 (3.6)
	Food poisoning	1 (3.6)
	Nausea	10 (35.7)
	Tongue discomfort	1 (3.6)
	Vomiting	2 (7.1)
General disorders and administration site conditions		
	Chest discomfort	1 (3.6)
	Fatigue	6 (21.4)
	Oedema peripheral	1 (3.6)
	Pain	1 (3.6)
	Pyrexia	1 (3.6)
	Temperature intolerance	2 (7.1)
Infections and infestations		
	Infected cyst	1 (3.6)
	Sinusitis	1 (3.6)
	Viral upper respiratory tract infection	1 (3.6)
Injury, poisoning and procedural complications		

	Arthropod bite	1 (3.6)
	Contusion	2 (7.1)
	Corneal abrasion	1 (3.6)
	Head injury	1 (3.6)
	Intentional product misuse	1 (3.6)
	Ligament sprain	1 (3.6)
	Sunburn	1 (3.6)
	Thermal burn	1 (3.6)
	Wound	1 (3.6)
Investigations		
	Body temperature fluctuation	1 (3.6)
Metabolism and nutrition disorders		
	Decreased appetite	3 (10.7)
	Dehydration	1 (3.6)
Musculoskeletal and connective tissue disorders		
	Arthralgia	1 (3.6)
	Joint stiffness	1 (3.6)
	Muscle tightness	12 (42.9)
	Musculoskeletal stiffness	2 (7.1)
	Myalgia	2 (7.1)
	Neck pain	2 (7.1)
	Pain in jaw	4 (14.3)
Nervous system disorders		
	Disturbance in attention	1 (3.6)
	Dizziness	4 (14.3)
	Headache	17 (60.7)
	Muscle contractions involuntary	1 (3.6)
	Nystagmus	5 (17.9)
	Paraesthesia	2 (7.1)
	Sensory disturbance	1 (3.6)
	Syncope	2 (7.1)
	Tension headache	1 (3.6)
Psychiatric disorders		
	Aggression	1 (3.6)
	Anxiety	4 (14.3)
	Bruxism	5 (17.9)
	Conversion disorder	1 (3.6)
	Depressed mood	1 (3.6)
	Dermatillomania	1 (3.6)
	Fear of eating	1 (3.6)
	Insomnia	8 (28.6)
	Panic reaction	1 (3.6)
	Suicidal ideation	4 (14.3)
	Suicide attempt	1 (3.6)
Renal and urinary disorders		
	Micturition urgency	1 (3.6)
Reproductive system and breast disorders		
	Dysmenorrhoea	1 (3.6)
	Menorrhagia	1 (3.6)
Respiratory, thoracic and mediastinal disorders		
	Cough	1 (3.6)
	Hyperventilation	1 (3.6)
Skin and subcutaneous tissue disorders		
	Hyperhidrosis	3 (10.7)

	Photosensitivity reaction	1 (3.6)
Vascular disorders		
	Orthostatic hypotension	1 (3.6)
	Peripheral coldness	1 (3.6)

Table 62: Treatment-Emergent Adverse Events by Body System during MDMA Sessions and Two Days Following in Sponsor-Supported Studies MP16 and MP17

SOC	Adverse Event Preferred Term	Day 0	Day 1	Day 2
Participants		28	28	28
Participants who reported an AE		26	13	8
		N (%)	N (%)	N (%)
Cardiac disorders				
	Palpitations	1 (3.6)	1 (3.6)	---
Ear and labyrinth disorders				
	Ocular discomfort	---	1 (3.6)	---
	Photophobia	1 (3.6)	---	---
	Vision blurred	1 (3.6)	---	---
	Visual impairment	1 (3.6)	---	---
Gastrointestinal disorders				
	Abdominal discomfort	2 (7.1)	1 (3.6)	---
	Aphthous ulcer	---	---	1 (3.6)
	Diarrhoea	1 (3.6)	---	---
	Dry mouth	2 (7.1)	---	---
	Eructation	1 (3.6)	---	---
	Nausea	9 (32.1)	2 (7.1)	---
	Tongue discomfort	1 (3.6)	---	---
	Vomiting	1 (3.6)	1 (3.6)	---
General disorders and administration site conditions				
	Chest discomfort	---	1 (3.6)	---
	Fatigue	1 (3.6)	1 (3.6)	3 (10.7)
	Oedema peripheral	1 (3.6)	---	---
	Pain	---	---	1 (3.6)
	Temperature intolerance	2 (7.1)	---	---
Infections and infestations				
	Sinusitis	---	---	1 (3.6)
Injury, poisoning and procedural complications				
	Thermal burn	---	---	1 (3.6)
Investigations				
	Body temperature fluctuation	1 (3.6)	---	---
Metabolism and nutrition disorders				
	Decreased appetite	2 (7.1)	1 (3.6)	---
	Dehydration	---	1 (3.6)	---
Musculoskeletal and connective tissue disorders				
	Arthralgia	1 (3.6)	---	---
	Joint stiffness	1 (3.6)	---	---
	Muscle tightness	12 (42.9)	---	---
	Musculoskeletal stiffness	1 (3.6)	---	---
	Myalgia	1 (3.6)	1 (3.6)	---
	Neck pain	---	1 (3.6)	---
	Pain in jaw	2 (7.1)	1 (3.6)	1 (3.6)
Nervous system disorders				
	Disturbance in attention	---	---	1 (3.6)
	Dizziness	3 (10.7)	1 (3.6)	---

	Headache	13 (46.4)	5 (17.9)	---
	Muscle contractions involuntary	1 (3.6)	---	---
	Nystagmus	5 (17.9)	---	---
	Paraesthesia	2 (7.1)	---	---
	Syncope (postural)	2 (7.1)	---	---
	Tension headache	1 (3.6)	---	---
Psychiatric disorders				
	Anxiety	1 (3.6)	1 (3.6)	---
	Bruxism	5 (17.9)	---	---
	Conversion disorder	---	---	1 (3.6)
	Depressed mood	---	1 (3.6)	---
	Insomnia	6 (21.4)	1 (3.6)	1 (3.6)
Renal and urinary disorders				
	Micturition urgency	1 (3.6)	---	---
Reproductive system and breast disorders				
	Dysmenorrhoea	1 (3.6)	---	---
Skin and subcutaneous tissue disorders				
	Hyperhidrosis	3 (10.7)	---	---
	Photosensitivity reaction	1 (3.6)	---	---
Vascular disorders				
	Orthostatic hypotension	1 (3.6)	---	---
	Peripheral coldness	1 (3.6)	---	---

In MP16 and MP17, a total of 28 participants were given an 80-120 mg dose of MDMA. The most commonly reported AE during experimental sessions was headache (46.4%), followed by muscle tightness (42.9%), nausea (32.1%), and fatigue (3.6%) (Table 62). These AEs were also most prevalent from experimental sessions to end of treatment: headache (60.7%), followed by muscle tightness (42.9%), nausea (35.7%), and fatigue (21.4%) (Table 61). Five counts of headache and four counts of fatigue were reported after the experimental session during Day 1 and Day 2 follow-up to indicate these AEs extended beyond day of drug administration. Other AEs reported by at least 10% of the study sample from experimental session to end of treatment included palpitations (10.7%), abdominal discomfort (10.7%), decreased appetite (10.7%), pain in jaw (14.3%), dizziness (14.3%), nystagmus (17.9%), anxiety (14.3%), bruxism (17.9%), suicidal ideation (14.3%), and hyperhidrosis (10.7%).

Social Anxiety in Autistic Adults

Table 63: Adverse Events by MedDRA (V. 17.1) System Organ Class (SOC) among Autistic Adults in Sponsor-Supported Phase 2 Study of MDMA-Assisted Psychotherapy MAA-1

SOC	Adverse Event Preferred Term[a]	Blinded 0 mg	Blinded 75-125 mg	Open-label 75-125 mg	12-month Follow-up
Participants per dose group		4	8	4	11
Participants who reported an AE		1	4	3	3
		N (%)	**N (%)**	**N (%)**	**N (%)**
General disorders and administration site conditions					
	Pain	---	---	---	1 (9.0)
	Pyrexia	---	1 (12.5)	---	---
Gastrointestinal disorders					
	Irritable Bowel Syndrome	1 (25.0)	---	---	---
Infections and infestations					
	Nasopharyngitis	---	1 (12.5)	---	1 (9.0)
	Sinusitis	1 (25.0)	---	---	---
	Upper respiratory infection	1 (25.0)	1 (12.5)	1 (25.0)	---
Injury, poisonings, procedural complications					
	Ligament injury	---	1 (12.5)	---	---
	Retinal injury	---	---	---	1 (9.0)
Musculoskeletal and connective tissue disorders					
	Back pain	---	---	1 (25.0)	---
	Myalgia	---	---	1 (25.0)	---
Nervous system disorders					
	Headache	---	1 (12.5)	---	---
	Syncope	---	---	---	1 (9.0)
Psychiatric disorders					
	Anxiety	---	1 (12.5)	---	---
	Depressed mood	---	2 (25.0)	---	---
	Depression	1 (25.0)	1 (12.5)	---	---
	Dissociation	---	---	---	---
	Panic attack	---	1 (12.5)	1 (25.0)	---
	Panic reaction	---	1 (12.5)	---	---
	Psychiatric symptom	---	---	---	---
	Suicidal ideation	1 (25.0)	2 (25.0)	1 (25.0)	---
Reproductive system and breast disorders					
	Dysmennorhea	---	1 (12.5)	---	---
Respiratory, thoracic and mediastinal disorders					
	Cough	---	1 (12.5)	1 (25.0)	---
	Oropharyngeal pain	---	---	1 (25.0)	---

[a] Codes derived from MedDRA v17. Only one instance of an individual event per subject after each experimental session and dose is reported.

In autistic adult participants with social anxiety, the frequency of any given AE in each study group was less than 25% (or 1-2 participants). The majority of AEs were psychiatric disorders (ten in active dose groups and two in the inactive placebo group), followed by infections and infestations (three in active dose groups and two in the inactive placebo group). Participants in the blinded 75-125 mg group reported the highest proportion of depressed mood (25%) and suicidal ideation (25%). There was no report of depressed mood in the blinded 0 mg group, although there was one report of depression. There was also one count of suicidal ideation in the blinded 0 mg group. The occurrence of depressed mood/ depression

and suicidal ideation in both blinded 0 mg and 75-125 mg groups suggest these AEs likely occurred independent of drug administration. There were three counts of panic attack/ panic reaction in only active dose groups, which might be attributed to drug administration. There were no severe adverse events reported in the study. However, these small sample sizes warrant further investigation to elucidate relationships between AEs and MDMA-assisted psychotherapy in autistic adults with social anxiety.

Anxiety Associated with Life-threatening Illness

Table 64: Adverse Events by MedDRA (v 17.1) System Organ Class (SOC) among Participants with Anxiety Associated with a Life-threatening Illness in Sponsor Supported Phase 2 Study of MDMA-Assisted Psychotherapy MDA-1

SOC	Adverse Event Preferred Term	Blinded 0 mg	Blinded 125 mg	Open-label 125 mg	12-Month Follow-up
Participants per dose group		5	13	17	17
Participants who reported an AE		2	11	7	9
		N (%)	**N (%)**	**N (%)**	**N (%)**
Cardiac disorders					
	Arrhythmia	---	---	1 (5.9)	---
Gastrointestinal disorders					
	Abdominal discomfort	---	1 (7.7)	---	---
	Abdominal pain	---	1 (7.7)	---	---
	Aphthous stomatitis	1 (20.0)	---	---	---
	Esophageal pain [Oesophageal pain]	---	---	---	---
	Nausea	---	1 (7.7)	---	---
	Oesophageal pain	---	---	1 (5.9)	---
	Diarrhea [Diarhoea]	---	1 (7.7)	---	---
General disorders and administration site conditions					
	Chest pain	1 (20.0)	---	---	---
	Fatigue	---	3 (23.1)	---	---
	Pain	1 (20.0)	1 (7.7)	---	---
Infections and Infestations					
	Influenza	---	2 (15.4)	---	---
	Meningitis	---	---	---	1 (5.9)+
	Oral herpes	---	---	1 (5.9)	---
	Post procedural cellulitis	---	---	---	1 (5.9)
	Sepsis	---	---	---	1 (5.9) +
	Tinea infection	---	1 (7.7)	---	---
	Upper respiratory tract infection	---	---	1 (5.9)	---
	Viral upper respiratory tract infection	1 (20.0)	---	---	---
Injury, poisoning and procedural complications					
	Contusion	---	2 (15.4)	---	---
	Fall	---	1 (7.7)	---	---
	Skeletal injury	1 (20.0)	---	---	---
	Skin abrasion	---	1 (7.7)	---	---
	Thermal burn	1 (20.0)	---	---	---
	Tooth fracture	---	1 (7.7)	---	---
Investigations					
	Heart rate irregular	---	---	1 (5.9)	---
	Weight decrease	---	1 (7.7)	---	---
Musculoskeletal and connective tissue disorders					
	Arthralgia	---	1 (7.7)	---	---
	Back pain	---	2 (15.4)	---	---
	Intervertebral disc degeneration	---	---	---	1 (5.9)
	Plantar fasciitis	1 (20.0)	---	---	---
	Muscle spasms	1 (20.0)	---	---	---
	Scleroderma	---	---	---	1 (5.9)
	Tenosynovitis stenosans	---	1 (7.7)	---	---
Neoplasms benign, malignant and unspecified					
	Chordoma	---	1 (7.7)+	---	---

	Intraductal proliferative breast lesion	---	---	---	1 (5.9)
	Invasive ductal breast carcinoma	---	---	---	1 (5.9) [+]
Nervous system disorders					
	Aphasia	---	---	---	1 (5.9)[+]
	Balance disorder	---	1 (7.7)	---	---
	Cerebrovascular accident	---	---	---	1 (5.9)[+]
	Clumsiness	---	1 (7.7)	---	---
	Muscle contractions involuntary	1 (20.0)	---	---	---
	Neuropathy peripheral	1 (20.0)	---	1 (5.9)	1 (5.9)
	Paraesthesia	---	1 (7.7)	---	1 (5.9)
	Sciatica	---	---	---	1 (5.9)
	Sinus headache	---	1 (7.7)	---	---
	Spinal cord paralysis	---	---	---	1 (5.9)[+]
	Tremor	---	---	1 (5.9)	---
Psychiatric disorders					
	Anxiety	---	1 (7.7)	2 (11.8)	---
	Bruxism	---	---	1 (5.9)	---
	Depressed mood	---	1 (7.7)	1 (5.9)	---
	Depression	---	1 (7.7)	---	1 (5.9)
	Dissociation	---	1 (7.7)	---	---
	Drug abuse**	---	---	---	1 (5.9)
	Hypomania	---	---	1 (5.9)	---
	Insomnia	1 (20.0)	2 (15.4)	4 (23.5)	---
Renal and urinary disorders					
	Nephrolithias	---	1 (7.7)	---	---
Reproductive system and breast disorders					
	Vaginal discharge	---	1 (7.7)	---	---
Respiratory, thoracic and mediastinal disorders					
	Hyperventilation	---	1 (7.7)	---	---
Skin and subcutaneous tissue disorders					
	Alopecia	---	1 (7.7)	---	---
	Pruritis	---	---	1 (5.9)	---
	Urticaria	---	1 (7.7)	1 (5.9)	---
Vascular disorders					
	Hot flush	---	---	1 (5.9)	---
	Lymphoedem	---	---	---	1 (5.9)

[a]AEs coded using MedDRA v17. Each adverse event reported once per subject per blinded or open-label period.
[+]AEs rated severe. Of the seven AEs rated severe, six AEs occurred in a single individual after cancer reoccurrence. The participant's last visit was the primary endpoint. The subject died prior to LTFU. A second subject experienced a severe AE during the long-term follow-up.
***LLT was nondependent use of hallucinogens, not a drug abuse disorder.*

Adverse events reported during the study of MDMA-assisted psychotherapy in participants with anxiety in response to facing life-threatening disorders included psychiatric disorders, nervous system disorders, gastrointestinal symptoms, and infections (Table 64). Of the seven AEs rated severe, six AEs occurred in a single individual after cancer reoccurrence. The participant's last visit was the primary endpoint. The subject died prior to LTFU. The other severe AE (invasive ductal breast carcinoma) occurred in a different participant during the long-term follow-up.

Overall, 40.0% of blinded 0 mg participants, 84.6% of blinded 125 mg participants, and 41.2% of open-label 125 mg participants reported any AE's during experimental sessions. The most common AE was insomnia, which was reported among 20.0% of blinded 0 mg participants,

15.4% of blinded 125 mg participants, and 23.5% of open-label 125 mg participants. Three counts of fatigue (23.1%) were reported only among blinded 125 mg participants. It may be possible drug administration was linked to insomnia and fatigue, which were also commonly reported AEs in other sponsor-supported study samples. In this sample, apart from insomnia, all other psychiatric AEs were reported by participants in active dose groups. Anxiety was reported in one blinded 125 mg participant and two open-label 125 mg participants, which was expected given the indication under study. There were single reports of bruxism, depressed mood, depression, dissociation, and hypomania in either the blinded 125 mg or open-label 125 mg groups.

Non-psychiatric AEs with more than one count included influenza (15.4%), contusion (15.4%), and back pain (15.4%), which occurred only among blinded 125 mg participants, although these events were likely unrelated to drug administration. Similarly, there were a total of nine participants, and a total of 16 AEs, that were reported at 12-month follow-up across all study participants. But, given the small sample sizes, it is difficult to conclude whether any occurrence of AE's one-year or more following experimental sessions were related to study treatment.

One subject in this study experienced a cascade of adverse events, including several SAEs, after completing the course of the main study and prior to or at long-term follow up that all followed from recurrence of chordoma. This event was expected given the participant's medical history. After the recurrence was noted, the subject received one additional experimental session. She then underwent debulking surgery, radiation, immunotherapy, and chemotherapy for treatment before significant deterioration (including spinal cord paralysis, spinal meningitis, septicemia, and cerebrovascular accident followed by aphasia and inability to speak) and subsequent death.

It is challenging to make comparisons or draw conclusions about nature or frequency of adverse events in this sample owing to small sample size. Psychiatric AEs in general, and anxiety in particular, are expected in this sample and with MDMA combined with psychotherapy that encourages confronting emotionally distressing material. It is also expected that participants diagnosed with a life-threatening illness may experience more severe AEs related to their medical history.

5.3.9.3 Serious Adverse Reactions

One SAR has occurred across nine sponsor-supported studies. SARs are serious adverse events possibly or probably related to MDMA administration. Not related serious adverse events are not presented in the IB. See Table 65 below for a summary.

Table 65: Serious Adverse Reactions in Sponsor-Supported Studies of MDMA-Assisted Psychotherapy Across Indications as of 31 May 2019

Dose	Comparator Dose (0-40 mg)	Active Dose (75-125 mg)	Open-label (100-150 mg)
	N	N	N
Cardiovascular			
Ventricular Extrasystoles (exacerbation)	---	---	1

One cardiac SAR has occurred within all sponsor-supported studies to date. In a PTSD study, subject 0811 experienced an increase in frequency of ventricular extrasystoles, a form of cardiac arrhythmia, on the day of his third and final experimental session with open-label 125 mg MDMA. The subject had no other signs and no symptoms of cardiac distress. In the absence of any symptoms of coronary insufficiency, the investigator judged the only medical measure necessary to be withholding the supplemental dose of MDMA. This was the final drug administration in Stage 2. No similar events were detected during the first two 125 mg experimental sessions, nor the two blinded experimental sessions with 30 mg MDMA in Stage 1. There was no evidence of acute cardiac damage or ischemia or underlying heart disease. At baseline during screening, the subject had one ventricular extrasystole on the baseline electrocardiogram (EKG), but the EKG was otherwise normal. The subject had a family history of his father having had a coronary artery bypass graft, which had prompted the subject to consult a cardiologist several years before study enrollment, and the cardiologist's note indicated that he did not suspect cardiovascular disease or see the need for further workup. Based on the medical history and clinical presentation of this subject, the investigator judged the SAR to be a moderate exacerbation probably related to drug administration, although since the subject was under observation when the event was noted, it cannot be determined if the same event occurred undetected prior to MDMA administration while the subject was not being monitored. The event required overnight monitoring in the hospital but did not lead to any adverse sequelae. He was given one dose of 25 mg metoprolol by the hospital physician but did not require any ongoing treatment. Serial cardiac isoenzymes, an echocardiogram and a nuclear stress test performed during the overnight hospital admission failed to show evidence of cardiovascular or other cardiac disease. Full recovery occurred 1 day after MDMA administration. Arrhythmia is described in sections 4.5 and 5.3.4 as an expected adverse effect of MDMA.

Anxiety-related psychiatric symptoms were the most commonly related AEs reported in MAPS supported studies. Most AEs were rated mild or moderate. MDMA produced several expected adverse events, collected as spontaneous reports on the day of an experimental session and for seven days afterwards, with most AEs subsiding before the end of the seven-day period. At least one post-drug AE occurred in nearly every system organ class, with most being general symptoms, nervous system disorders or psychiatric disorders. A single SAR of a cardiac event, as described above, has been reported as of May 31, 2019.

5.3.10 Abuse Potential

Subjective Effects

MDMA produces anxiolytic and prosocial effects, which could counteract avoidance and hyperarousal. These subjective effects of MDMA are hypothesized to create a desirable psychological state that enhances the therapeutic process in treating PTSD and other anxiety disorders. Findings using both subjective and objective indices of mood alterations suggest that MDMA generates prosocial feelings and mental states in humans in controlled laboratory settings. These effects may also be associated with determining the abuse liability of MDMA. Subjective effects of moderate doses of MDMA in controlled laboratory settings to healthy non-dependent volunteers, with a range of Ecstasy use history, have been reported in 28 publications summarized in a NIDA-funded review (N=657) [709]. These self-reported ratings include a broad range of mood states with relevance to social behavior.

Table 66: Summary of Ecstasy Use History and Subjective Effects of MDMA Among Healthy Volunteers in Controlled Studies Conducted Without Sponsor Support

Sample Size (N)	Mean # of Times Used Ecstasy (SD)	MDMA Doses	Mean Age (SD)	Finding by Dose[2,3]	Study
9	63.9 (94.9)	0.75 mg/kg, 1.5mg/kg	24.0 (3.2)	1.5mg/kg ↑ VAS Sociable, Friendly	Bedi et al. 2009 [26]
21	15 (23.1)	0.75 mg/kg, 1.5mg/kg	24.4 (4.9)	1.5mg/kg ↑ VAS Loving, Playful, POMS Friendly, ↓ fear recognition 0.75 mg/kg ↑ VAS Lonely	Bedi et al. 2010 [37]
8	23.0[4]	75 mg, 125 mg	26.5[4]	125 mg: ↑ ARCI sedation, dysphoria, amphetamine-like ↑ VAS High, body perception changes, confusion, difficulty concentrating ↑ POMS Elation, positive mood 75 mg: ↑ ARCI dysphoria, VAS euphoria, drunken	Cami et al. 2000 [8]
15	110.5 (175.3)	100 mg	21.1 (1.7)	↑ BLMRS Gregarious, Amicable, positive correlation with plasma oxytocin level	Dumont et al. 2009 [710]
36	4-40[1]	0.75 mg/kg, 1.5mg/kg	24.6 (4.7)	0.75 mg/kg, 1.5mg/kg ↑ VAS Loving ↓ Cyberball mood & self-esteem effect of social rejection; 1.5mg/kg ↑ estimate of rejection	Frye et al. 2014 [666]
16	0 (-)	1.7mg/kg	26.0 (2.5)	↑ EWL Self-confidence, Extroversion	Gamma et al. 2000 [28]
8	5-200[1]	0.5mg/kg, 1.5mg/kg	24-39[1]	1.5mg/kg ↑ VAS Confident	Harris et al. 2002 [10]
16	≤ 5	125 mg	25.7 (5.5)	↑ VAS Closeness to Others, AMRS Extroversion	Hysek et al. 2011 [635]
48	≤ 5	125 mg	26.0 (5.0)	↑ VAS Open, Closeness to Others, Talkative	Hysek et al. 2012a [30]
16	≤ 5	125 mg	25.4 (4.9)	↑ VAS Open, Closeness to Others	Hysek et al. 2012b [229]

16	0	125 mg	26.1 (6.0)	↑ VAS Open, Closeness to Others, Talkative, AMRS Extroversion	Hysek et al. 2012c [232]
16	≤ 5	125 mg	25.8 (3.3)	↑ AMRS Extroversion, Self-confidence	Hysek et al. 2013 [711]
32	≤ 5	125 mg	25.0 (3.0)	↑ VAS Open, Closeness to Others, AMRS Extroversion ↑ MET Emotional empathy	Hysek et al. 2014a [19]
16	≤ 5	125 mg	24.8 (2.6)	↑ VAS Closeness to Others, AMRS Extroversion	Hysek et al. 2014b [599]
8	20.0[4]	1.0mg/kg, 1.5mg/kg	25.0[4]	↑ VAS Friendly	Johanson et al. 2006 [712]
14	13.5 (12.0)	0.75 mg/kg, 1.5mg/kg	25.4 (3.7)	1.5mg/kg ↑ VAS Friendly, Loving, Sociable	Kirkpatrick et al. 2014a [31]
65	G1: 13.5 (10.6) G2: 18.1 (12.0)	0.75 mg/kg, 1.5mg/kg	G1: 24.1 (4.1) G2: 23.1 (3.5)	0.75,1.5mg/kg ↑ VAS Friendly, Loving, Playful, Sociable 1.5mg/kg ↑ VAS Lonely	Kirkpatrick et al. 2014b [71]
32	SOL: 14.5 (22.2) RAP: 18.4 (13.1) OPP: 20.9 (21.5)	0.5mg/kg, 1.5mg/kg	SOL:24.7 (2.7) RAP:25.7 (4.8) OPP:24.5 (3.3)	SOL: 1.0mg/kg ↑ VAS Insightful RAP: 1.0mg/kg ↑ VAS Insightful, Loving OPP: 0.5, 1.0mg/kg ↑ VAS Insightful, 1.0mg/kg ↑ VAS Loving	Kirkpatrick & de Wit 2015 [667]
8	≥ 5	1.0mg/kg, 1.6mg/kg	21.1 (0.8)	1.6mg/kg ↑ VAS Closeness to Others	Kolbrich et al. 2008 [7]
14	65.8 (134.5)	75 mg	23.4 (3.0)	↑ POMS Friendliness	Kuypers et al. 2011 [657]
17	18.0 (33.0)	75 mg	21.0 (1.2)	↑ POMS Friendliness	Kuypers et al. 2013 [650]
16	N=13 naïve; N=3 unknown	1.5mg/kg	27.4 (4.4)	↑ AMRS Extroversion, Self-confidence	Liechti et al. 2000a [630]
14	N=12 naïve; N=2 unknown	1.5mg/kg	26.0[4]	↑ AMRS Extroversion, Self-confidence	Liechti et al. 2000b [634]

30	≤ 5	75 mg	24.0 (4.2)	↑ VAS Openness, Trust, Close to Others	Schmid et al. 2014 [36]
12	14.5[4]	1.0mg/kg, 2.0mg/kg	22.3[4]	2.0mg/kg ↑ VAS Friendly, Social, Talkative	Tancer and Johanson 2003 [12]
8	28.6[4]	1.5mg/kg	23.9[4]	↑ VAS Talkative, Friendly, not effected by fluoxetine co-admin	Tancer and Johanson 2007 [633]
17	72.4[4]	75 mg	22.8 (2.8)	↑ POMS Friendliness	van Wel et al. 2012 [100]
101	13.3 (10.5)	0.75 mg/kg, 1.5mg/kg	24.1 (4.2)	↑ VAS Playful, Loving	Wardle et al. 2014 [41]
36	10.2 (8.2)	0.75 mg/kg, 1.5mg/kg	24.6 (4.7)	↑ VAS Loving	Wardle and de Wit 2014 [42]

Source: [672, 709]
[1] These studies reported range (min-max) in lieu of mean (SD)
[2] ↑ = Drug increased function relative to placebo, ↓ = Drug decreased function relative to placebo
[3] ARCI= Addiction Research Center Inventory, AMRS=Adjective Mood Rating Scale, FERT= Facial Emotion Recognition Task, BOLD=Blood Oxygen Level Dependent, MET=Multifaceted Empathy Test, SVO=Social Value Orientation Test, mFER=morphed Facial Emotion Recognition Task, RMET=Reading the Mind in the Eyes Test, MASC=Movie for the Assessment of Social Cognition, MJT=Moral Judgment Task, DANVA=Diagnostic Analysis of Nonverbal Accuracy, DEIT=Dynamic Emotional Identification Task, IPT=Interpersonal Perception Task (Modified), POMS=Profile of Mood States, VAS=Visual Analog Scale, G1= Group 1, G2= Group 2
[4] SD not presented in original publication

As presented in Table 66, participants endorsed the following verbatim terms as VAS items: feeling loving, talkative, extroverted, sociable, self-confident, friendly, playful, open, trusting, close to other people, and emotionally concerned. MDMA's subjective prosocial effects may be enhanced in group settings when other individuals have also been administered MDMA in laboratory studies. Increased feelings of loneliness may have resulted from testing conditions where participants receive MDMA in comparative isolation; however, these effects are not dependent on a permissive environment. From latent speech analysis and self-report data, "want more drug" ratings were predictive of prosocial effects, supporting this as the basis for moderate abuse liability of MDMA in healthy volunteers [709, 713].

A prospective pooled analysis of eight controlled non-sponsor supported clinical studies, was conducted in an overall sample of 139 healthy nondependent individuals (mean age 24.9, SD:4.1). In participants receiving 75 mg (N=29) or 125 mg MDMA (N=110), subjective "any drug effect" ratings were significantly higher ($p<0.05$) at 0.6 hours post-drug in poor metabolizers with CYP2D6 polymorphisms, which leads to 15% elevated C_{max} of MDMA and 50% elevated C_{max} of MDA. "Drug liking" ratings were also significantly higher in poor metabolizers at 0.6 hours ($p<0.001$) and one-hour post-drug ($p<0.01$) [714]. However, these effects were no longer significant at 1.5 hours post-drug.

In a study conducted without sponsor support of 22 individuals (mean age 23.6) with a history of stimulant drug use (more than six times) and previous Ecstasy use (more than 3 times) in a double-blind randomized study, participants were asked to identify 2.0 mg/kg MDMA and serotonergic drug *meta*-chlorophenylpiperazine (*m*CPP), which has both serotonin releasing and

post-synaptic effects. At 1- 2.1 mg MDMA, 80% of participants identified MDMA as an empathogen or hallucinogen and only 20% identified MDMA as a stimulant [673]. In contrast, results were mixed with 0.25-0.75 mg/kg *m*CPP, with results varying from hallucinogen to stimulant to sedative depending on the dose. On the "drug liking" VAS, 1.6 mg/kg ($p<0.004$) and 2.1 mg/kg MDMA ($p<0.008$) were significantly higher than placebo, whereas *m*CPP ratings were not significantly higher than placebo at any dose [673]. In another study in a sample of 74 largely drug-naïve participants receiving MDMA in a controlled laboratory setting, Liechti and colleagues stated that "none of the participants expressed any interest in taking MDMA as a recreational drug" after receiving MDMA [11]. Collectively, these findings support the interpretation that MDMA received in controlled settings is inherently different than MDMA taken in recreational settings, and abuse liability of MDMA-assisted psychotherapy should be evaluated in its intended setting and population for clinical use.

Drug Discrimination and Stimulant Comparison

The abuse liability of MDMA has been investigated in healthy volunteers utilizing a drug discrimination paradigm in two studies. The first study was in healthy nondependent volunteers with moderate MDMA experience (mean age 22.3) with a history of stimulant drug use (more than 6 times) and previous Ecstasy use (mean 14.5 times) comparing placebo, 10 mg and 20 mg *d*-amphetamine, 0.5 mg/kg and 0.75 mg/kg *m*CPP and 1.0 mg/kg and 2.0 mg/kg MDMA in a within-subject design (N=12). In this study, MDMA and *d*-amphetamine had similar reinforcing effects, and both were more than the effects of *m*CPP [12]. In humans trained to discriminate in a three-way procedure among 20 mg *d*-amphetamine, 0.75 mg/kg *m*CPP, and placebo, both 1.0 mg/kg and 1.5mg/kg MDMA was reported by half the participants to be like amphetamine and half like *m*CPP (N=22). Individuals who identified MDMA to be more like amphetamine were more sensitive to the subjective effects of all drugs, and they were more experienced with using Ecstasy and stimulants prior to the study [712]. Table 42 below presents a summary of studies with direct comparisons of MDMA vs. stimulants. Seven of ten studies found differences between MDMA vs. stimulants, with doses of 2.0 mg/kg MDMA and higher having more similar effects to stimulants.

Table 67: Summary of Selected Effects in Controlled Clinical Studies Comparing MDMA and Stimulants Among Healthy Volunteers Conducted Without Sponsor Support

Pre-study Ecstasy Use History			During Controlled MDMA Administration		During Controlled Stimulant Administration	
Sample Size (N)/ Study	Mean # of Times Used Ecstasy (SD)	Mean Age (SD)	MDMA Doses Tested	Finding by Dose[c]	Stimulant Doses Tested	Finding by Dose[c]
8/ Cami et al. 2000 [8]	23.0[c]	26.5[c]	75 mg, 125 mg	125 mg: ↑ ARCI sedation, dysphoria, amphetamine-like ↑ VAS High, body perception changes, confusion, difficulty concentrating ↑ POMS elation, positive mood 75 mg: ↑ ARCI dysphoria ↑ VAS euphoria, drunken	*d*-Amph 40 mg	↑ ARCI amphetamine-like, energy, intellectual efficiency ↓ ARCI sedation
21/ Bedi et al. 2010 [37]	15 (23.1)	24.4 (4.9)	0.75 mg/kg, 1.5mg/kg	1.5mg/kg ↑ POMS Friendly, ↓ fear recognition No effect on VAS Social	Meth 20 mg	No effect on fear recognition or POMS Friendly ↑ VAS Social
13/ Bedi et al. 2014 [40]	2 (-)	18-38[a]	0.75 mg/kg, 1.5mg/kg	1.5mg/kg ↑ social words	Meth 20 mg	No effect on social words
16/ Hysek et al. 2014b [599]	≤ 5	24.8 (2.6)	125 mg	↑ VAS Closeness to Others, AMRS Extroversion ↓ recognition: negative emotions	Methylph 60 mg	↑ recognition: negative emotions
8/ Johanson et al. 2006[712]	20.0[c]	25.0[c]	1.0mg/kg, 1.5mg/kg	↑ VAS Friendly	*d*-Amph 20 mg	↑ VAS Friendly
11/ Kirkpatrick et al. 2012[53]	2.1 (1.8) per month	29.3 (50)	100 mg	↑ VAS Social, Talkative	Meth 20 mg 40 mg	20 mg ↑ VAS Social 40 mg ↑ VAS Social, Talkative
30/ Schmid et al. 2014 [36]	≤ 5	24.0 (4.2)	75 mg	↑ MET Emotional empathy for positive situations ↓ recognition: sadness	Methylph 40 mg	No effect on emotional empathy for positive situations or recognition of sadness
12/ Tancer, Johanson	14.5[c]	22.3[c]	1.0mg/kg, 2.0mg/kg	2.0mg/kg ↑ VAS Friendly, Social,	*d*-amph 10 mg,	20 mg ↑ VAS Friendly

2003 [12]				Talkative	20 mg	
30/ Schmid et al. 2015 [669]	≤ 5	24.0 (4.2)	75 mg	No effect on ratings of erotic images	Meth 40 mg	↑ ratings of erotic images
11/Marrone et al. 2010[715]			100 mg	No effect on speech quantity ↓ fluency	Meth 20 mg 40 mg	↑ speech quantity, fluency

Source: Appendix 7 [672]
Abbreviations: d-Amph=d-Amphetamine, Meth=Methamphetamine, Methlyph=Methylphenidate, ARCI= Addiction Research Center Inventory, FERT= Facial Emotion Recognition Task, BOLD=Blood Oxygen Level Dependent, MET=Multifaceted Empathy Test, SVO=Social Value Orientation Test, mFER=morphed Facial Emotion Recognition Task, RMET=Reading the Mind in the Eyes Test, MASC=Movie for the Assessment of Social Cognition, MJT=Moral Judgment Task, DANVA=Diagnostic Analysis of Nonverbal Accuracy, DEIT=Dynamic Emotional Identification Task, IPT=Interpersonal Perception Task (Modified), POMS=Profile of Mood States

[a] These studies reported range (min-max) instead of mean(SD)
[b] ↑ = Drug increased function relative to placebo, ↓ = Drug decreased function relative to placebo
[c] SD not presented in original publication

A dose of 100 mg MDMA was directly compared to 20 mg and 40 mg methamphetamine in a placebo-controlled blinded in-patient study measuring pharmacokinetics, physiological effects, and subjective effects (N=11). The study was in healthy non-dependent volunteers (mean age 29.3, SD:50) with current stimulant (4.2 days/month) and Ecstasy use (2.1 days/month). Both drugs had a similar time course of effects with oral administration. Plasma levels peaked at 3 hours and declined over the 24-hour period post-administration, with minor levels of drug remaining above baseline in plasma at the end of this period. Both drugs enhanced cardiovascular parameters, ratings of stimulation, euphoria, and mood, and decreased food intake. Methamphetamine, but not MDMA, caused significant residual pulse and DBP elevation at the end of the 24-hour period ($p<0.01$). MDMA did not enhance performance, indicating the absence of this contributor to reinforcing effects, in contrast to methamphetamine. Methamphetamine produced primarily positive effects (Good Drug Effect, Stimulated, Desire to Take Again, Drug Liking), whereas MDMA had some positive (Good Drug Effect, Stimulated) and some negative effects (Bad Drug Effect, Can't Concentrate, Tired, Sleepy). Only methamphetamine disrupted sleep, objectively measured via Actigraphy, and increased tiredness. MDMA did not disturb sleep, and instead facilitated ability to more readily fall asleep. As most participants were unable to correctly identify the drug received, and important confound is that experienced Ecstasy users may have based their opinions about MDMA on material of low purity and unknown dose. The sponsor has been given permission to access primary data for this study under IND #074039. Taken together, these observations and other studies support distinct differences in subjective and reinforcing effects, supporting a lower abuse liability for MDMA than stimulants.

Prevalence of Dependence

There have been no reports of MDMA dependence developing after participation in controlled MDMA studies. In the absence of drug dependence studies on MDMA, a summary of Ecstasy dependence studies is presented. Ecstasy is purported to contain MDMA, but in the majority of pills submitted for anonymous testing, no MDMA is found and/or impurities abound. Some adulterants, such as amphetamines, that are commonly found in Ecstasy tablets may be responsible for the dependence and cravings associated with Ecstasy [716]. Research of Ecstasy dependence comes from a combination of published studies with assessment of symptoms based

on the Composite International Diagnostic Interview, the *DSM-4*, and/or the Severity of Dependence Scale [717]. One study with a non-representative sample (N=173) including participants recruited from substance abuse programs reported 30% had used Ecstasy and of these, 43% met DSM-IV criteria for dependence (N=52) [718]. In a large Australian sample (N=329), approximately 25% of polydrug users wanted to reduce their Ecstasy use and 20% had received treatment for an Ecstasy-related problem, although this sample likely had "an over-representation of chaotic intravenous polydrug users [719]."

In a study of self-reported cravings in Ecstasy users utilizing an 8-item questionnaire (N=169), a negative mean score for participants exposed to Ecstasy-related cues was obtained, indicating that participants disagreed with statements reflecting craving on average. In a subscale analysis, about 50% of survey participants agreed on some level with two of eight statements that supported the craving to use Ecstasy after exposure to Ecstasy-related cues, suggesting that some respondents may experience a low level of craving for Ecstasy [716]. It also appears that Ecstasy has fewer or less intensely rewarding effects than stimulants, and even heavy Ecstasy users fail to report the intensive patterns of use seen with other stimulants [2, 4, 720]. Based on two structural analyses, Ecstasy dependence is bifactorial [721]. Although Ecstasy dependence does have a compulsive use factor as well as an escalating use factor, withdrawal symptoms do not include significant physical symptoms such as those occurring with alcohol, cocaine, methamphetamine, opioids, and tobacco [722, 723]. In a prospective longitudinal study conducted over an average of 42 months in a representative sample of Munich residents aged 14 to 24 (N=2446), only 1.0% were diagnosed with Ecstasy abuse and 0.6% with dependence. A substantial decline in use factors was noted 12+ months later, suggesting that Ecstasy use is a self-limiting transient phenomenon in many cases [724]. Features of Ecstasy abuse and dependence in human healthy volunteers are consistent with nonclinical findings in self-administration studies of moderate abuse liability that is greater than that for serotonergic hallucinogens, but less than that for stimulants (see Section 12.5).

When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants in a study conducted outside of sponsor support, Liechti and colleagues stated that "none of the participants expressed any interest in taking MDMA as a recreational drug" after receiving MDMA in a controlled research setting [11]. When assessed in terms of willingness to choose money over receiving the drug, participants previously experienced with Ecstasy provided similar responses to 2 mg/kg MDMA and 20 mg d-amphetamine, a sign of having reinforcing effects [673]. A study that enrolled participants with a history of Ecstasy use (4 to 40 occasions) found that only self-reported feelings of playfulness were associated with participants' desire to take MDMA in a controlled research setting [42].

In addition to the extensive published clinical and nonclinical literature on the abuse liability potential associated with MDMA, the sponsor has collected self-reported Ecstasy use data at long-term follow-up and assessed the AEs for signals of abuse. At screening participants who met DSM-4 criteria for active substance abuse for 60 days prior to enrollment were excluded from participation in all but one study, where active substance abuse for 180 days prior to enrollment was excluded (MP-4). Participants who had used Ecstasy more than five times within the past 10 years prior to enrollment were also excluded. As a part of the Informed Consent process, study staff informed participants about the difference between Ecstasy and MDMA used in research studies. Table 43 below summarizes self-reported Ecstasy use data (recreational drug purported to be MDMA, unknown purity and dose) pre-study at least six months prior to study entry vs. long-term follow-up at 12+ months in Phase 2 PTSD clinical trials. Participants were encouraged to report use honestly under coverage of a Certificate of Confidentiality from FDA.

Table 68: Pre-Study Ecstasy Use Compared to Ecstasy Use Based on Long-term Follow-up Questionnaire After All Participants Received Two to Three Blinded or Open-label Active Dose MDMA-Assisted Psychotherapy for Treatment of PTSD

Pre-study Ecstasy Use				Long Term Follow-Up Post MDMA			
	Enrolled N	People Reporting Pre-study Use N (%)	Mean # of Times Used (SD)	LTFU N	People Reporting Post-Study Use N (%)	Mean # of Times Used (SD)	Context of Use
MP1							
	23	10 (43.5%)	2.0 (1.25)	19[a]	1 (5.3%)	1 (-)	Attempted Therapeutic
MP2							
	14	1 (7.1%)	3.0 (-)	11[b]	0 (0.0%)	-	-
MP4							
	6	0 (0.0%)	-	6	0 (0.0%)	-	-
MP8							
	26	6 (23.1%)	2.7 (1.21)	24	2 (8.3%)	1 (-)	Attempted Therapeutic; Recreational
MP9							
	10	2 (20.0%)	1.0 (0.00)	8	2 (25.0%)	1.5 (0.71)	Attempted Therapeutic; Recreational
MP12							
	28	13 (46.4%)	2.6 (1.71)	24	3 (12.5%)	1.3 (0.58)	Attempted Therapeutic; Recreational
All Studies Pooled							
	107	32 (29.9%)	2.3 (1.43)	92	8 (8.7%)	1.3 (0.49)	Attempted Therapeutic; Recreational

[a] CAPS data available from N=16 only, questionnaire available from N=19
[b] One subject died prior to completing long-term follow-up due to progression of cancer.

In sponsor-supported PTSD studies in 107 participants treated with MDMA-assisted psychotherapy in a controlled clinical setting, 29.9% (32 of 107) of participants had tried Ecstasy at least six months prior to enrollment, with U.S. samples demonstrating a higher prevalence of use than international studies. Participants reported using Ecstasy an average (SD) of 2.3 (1.43) times. At long-term follow-up, 8.7% of participants (8 of 92) reported use across studies (see Table 43). Six of the eight participants had used Ecstasy prior to the study. Of these participants, most were attempting to recreate a therapeutic experience, and none indicated a desire to repeat this. In addition to self-report data, urine drug screens specific for MDMA were performed at random and two, six and 12 months after the final experimental session during one study (MP-2, N=12). All were negative, supporting the observation that study participants did not seek out MDMA or Ecstasy after taking part in the study [45]. In addition to data on Ecstasy use at follow up, AEs were reviewed across Phase 2 studies, the sponsor found a low rate of clinically significant AEs supporting drug dependence, intentional drug misuse, substance abuse, and (<2%) of secondary terms that reflect acute intoxication. One instance of "drug abuse" was reported in study MDA-1 in a population with anxiety associated with life-threatening illness. This AE referred to a single nondependent use of a hallucinogen, which MedDRA coding places under the preferred term 'drug abuse" but does not indicate a substance use disorder. Data drawn from sponsor-supported studies suggests that MDMA has low abuse liability when given within a controlled, psychotherapeutic setting.

5.4 5.4 Efficacy of MDMA Across Populations

5.4.1 PTSD

Completed sponsor-supported Phase 2 studies of MDMA-assisted therapies employed recognized clinician-administered gold-standard measures of the condition or symptoms. The primary outcome measure of efficacy for studies of MDMA-assisted psychotherapy for PTSD to date is the Clinician Administered PTSD Scale (CAPS-IV) following DSM-IV, an established semi-structured interview conducted by a trained clinician [725-727]. The Total Severity CAPS-IV score encompasses frequency and intensity scores for three symptom domains: re-experiencing, avoidance and hyperarousal. An independent rater that does not see the participants during any of the psychotherapy sessions administers the CAPS at baseline and at the primary endpoint (1 or 2 months after blinded MDMA-assisted psychotherapy sessions). Secondary endpoints include an assessment 1 to 2 months after a third experimental session and 12 months after the last treatment.

Analyses of the CAPS-IV Total Severity scores at the primary endpoint after two experimental sessions in MP-1 found participants receiving MDMA-assisted psychotherapy experienced a clinically and statistically significant decline in PTSD symptoms compared to placebo-assisted psychotherapy [43]. Placebo subject scores dropped 20.5 points 2 months after the second experimental session while MDMA subject CAPS scores dropped 58.6 points. The second study (MP-2) found results similar to the MP-1 study, but improvement after three blinded experimental sessions with 125 mg MDMA was numerically but not statistically superior to the 25 mg MDMA comparator dose [45]. CAPS scores declined 15.7 points over time for the eight participants given 125 mg MDMA; on the other hand, CAPS scores increased slightly by 4.3 points over time for the four participants given comparator dose.

Table 69 below show pooled mean Total Severity CAPS-IV scores for sponsor-supported studies (MP-1, MP-2, MP-4, MP-8, MP-9, MP-12). Since data collection is still in progress, formal analyses have yet to be executed, but data trends are the same as published reports, with a medium to large effect size of active dose MDMA-assisted psychotherapy depending on number of experimental sessions completed. Table 44 below depicts mean Total Severity CAPS-IV scores at Baseline, 1 to 2 months after the second experimental session (Primary Endpoint), and 1 to 2 months after the third experimental session (End of Stage 1). All data from participants who received 75 mg, 100 mg, or 125 mg during Stage 1 blinded sessions were pooled into one active dose group, while data from participants who received 0 mg, 25 mg, 30 mg, or 40 mg were pooled into one comparator dose group. Despite slight differences in study designs, including length of time post second experimental session to outcome assessment (three to eight weeks), and language of the CAPS (English or translated), these results demonstrate reproducibility and generalizability across multiple international studies of MDMA-assisted psychotherapy in the treatment of chronic PTSD. Placebo and comparator groups cross over to Stage 2 after the Primary Endpoint; therefore, CAPS was not administered at the End of Stage 1 for these groups. Active dose groups (100 mg and 125 mg) do not crossover, hence no data for Stage 2 endpoints. Long-term follow-up data collection is ongoing.

Table 69: Mean CAPS-IV Total Severity Scores in Stage 1 of Phase 2 Sponsor-Supported Studies of MDMA-Assisted Psychotherapy for PTSD

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)
0-40 mg Blinded	81.3 (15.89) N=31	69.7 (21.98) N=31	---
75-125 mg Blinded	85.8 (19.3) N=74	47.4 (30.56) N=72	40.8 (26.22) N=51
Open-label 125 mg	98.5 (27.58) N=2	56.5 (37.48) N=2	---
Dose Stage 2	**Secondary Endpoint Mean (SD)**	**End of Stage 2 Mean (SD)**	**12-month Follow-up Mean (SD)**
Open-label 100-125 mg	37.9 (20.58) N=30	34.6 (23.48) N=27	---
All Participants	---	---	34.5 (24.23) N=90

Across studies, CAPS-IV scores are downward trending at the primary endpoint, after two experimental sessions of MDMA-assisted psychotherapy. Primary endpoint results after active doses of 75-125 mg initial dose, with an optional supplemental half-dose administered 1.5 to 2.5 hours later, appear lower than placebo or comparator dose results after two experimental sessions. Two-month follow-up results at the End of Stage 1 after a blinded or open-label third experimental session demonstrate further mean decreases in CAPS score, signaling potential advantage of a third session that will be further explored in a blinded three session treatment model of MDMA-assisted psychotherapy in Phase 3.

Across studies, CAPS-IV scores trended downward at the secondary endpoint after two open-label experimental sessions of MDMA-assisted psychotherapy, consistent with Stage 1 results. Secondary endpoint results in the crossover set receiving an active dose of 100-125 mg MDMA after receiving comparator dose or placebo in Stage 1 are in range with participants receiving active doses in Stage 1. Twelve-month follow-up results after all participants have received active dose MDMA in either Stage 1 or Stage 2 suggest that the gains during the treatment period are durable for many participants and the integration process may continue to lead to further improvement of PTSD symptoms overtime.

5.4.2 Social Anxiety in Autistic Adults

The primary outcome measure for the study of social anxiety in people on the autism spectrum is the Liebowitz Social Anxiety Scale (LSAS). This observer-blind measure is an established clinician-administered measure of social anxiety, assessing fear and avoidance in different situations. The LSAS consists of 24 items, with each item rated on a four-point scale (from 0 to 3), with subscales for performance fear, performance avoidance, social fear, and social avoidance.

Data is being collected on the effects of two sessions of MDMA-assisted therapy in people on the autism spectrum with social anxiety symptoms. Improvement in LSAS scores from Baseline to the Primary Endpoint was significantly greater for MDMA group compared to the placebo group (P = 0.037), and placebo-subtracted Cohen's *d* effect size was very large (*d*=1.4, CI: -0.074, 2.874). Change in LSAS scores from Baseline to 6-month follow-up showed similar positive results (P = 0.036), with a Cohen's *d* effect size of 1.1 (CI: -0.307, 2.527). The study safety and efficacy data were published [728].

Table 70: Liebowitz Social Anxiety Total Scores at Endpoints

	Placebo (n = 4)		MDMA (n = 8)[c]
Primary Efficacy Variable			
LSAS Total Score, mean (SD)			
Baseline	83.3 (11.9)		91.8 (15.8)
Primary Endpoint	64.0 (13.3)		46.4 (15.2)
Change[a]	-19.3 (18.8)		-44.1 (14.8)
P value[a]		0.037	
LSAS Total Score, mean (SD)			
Baseline	83.3 (11.9)		91.8 (15.8)
6-month follow-up	60.0 (17.4)		42.9 (20.4)
Change[a]	-23.3 (18.0)		-47.7 (14.7)
P value[a]		0.036	

[a] Change from Baseline

5.4.3 Anxiety Associated with Life-Threatening Illness

MAPS is studying the effects of MDMA-assisted psychotherapy on people experiencing anxiety as they face of a potentially life-threatening illness. A manuscript containing results has been submitted for publication and currently under peer review. Once published results will be presented in the IB.

6.0 Summary of Data and Guidance for the Investigator

MDMA is a psychoactive compound that affects mood, perception, and increases prosocial feelings. The sponsor is investigating use of this compound as an adjunct to psychotherapy for treating PTSD, social anxiety in people on the autism spectrum, and anxiety related to a life-threatening illness. Researchers with and without sponsor support have conducted *in vitro* and *in vivo* non-clinical and clinical studies with MDMA, and additional clinical trials are ongoing. Currently, MDMA is listed as a Schedule I controlled substance in the U.S. and is not permitted for medical use outside of research settings. Psychotherapists in the U.S. began to use MDMA as an adjunct to psychotherapy in the mid to late 1970s, and narrative accounts describe therapeutic use prior to its scheduling. MDMA was administered to thousands of people in a therapeutic setting prior to scheduling and has been administered to more than 1800 people in controlled research settings as of May 31, 2019. These studies have demonstrated that MDMA can be safely administered to people with PTSD in a controlled clinical setting.

In comparison to anxiolytics, antidepressants, and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to psychotherapy with rapid onset in some participants. A limited number of exposures to MDMA, spaced approximately 1 month apart at moderate doses, are sufficient to obtain therapeutic outcomes. This intermittent dosing mitigates AE frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA, the sponsor concludes that it appears favorable to pursue the research of MDMA as a medicine used as an adjunct to psychotherapy.

6.1 Pharmacology

The pharmacology of MDMA is complex, it activates multiple signaling cascades in the body. The formulation of the investigational product in Phase 2 studies consists of a gelatin capsule consisting of racemic white crystalline MDMA, at doses ranging from 12.5 mg to 150 mg, compounded with alpha-lactose, and administered orally. Due to a wide range of responses to identical mg/kg dosing between individuals, possibly as a result of inconsistent relationship between body weight and pharmacodynamic activity, the sponsor's human trials use fixed doses between approximately 1 and 4 mg/kg (active fixed doses range from 75 mg to 225 mg cumulative with supplemental dosing, assuming a 70 kg individual) to achieve a more consistent response between participants. In humans, onset of effects occurs approximately 30 to 60 minutes after administration, and peak effects occur 75 to 120 minutes after administration. Duration of effects lasts 3 to 6 hours, which extends to 6 to 8 hours with supplemental dosing.

The pharmacokinetics of MDMA in humans has been characterized using oral doses up to 150 mg MDMA in humans. MDMA disposition in the body follows nonlinear pharmacokinetics. MDMA is metabolized in the liver by several enzymes. Active doses of MDMA may saturate CYP2D6 function for an extended period, with function normalizing up to 10 days post-MDMA. The enzymes CYP1A2, COMT, and MAO are also be involved in the metabolism of MDMA. MDMA is metabolized by *N*-demethylation to MDA. The parent compound and MDA are further *O*-demethylated to HHMA and HHA, respectively. Both HHMA and HHA are subsequently *O*-methylated mainly to HMMA and HMA. These four metabolites, particularly HMMA and HMA, are known to be excreted in the urine as conjugated glucuronide or sulfate metabolites. The elimination half-life of active MDMA doses is 7 to 9 hours.

MDMA is a triple monoamine reuptake inhibitor, which concomitantly promotes carrier-mediated release, inhibits reuptake, and extends duration of serotonin, norepinephrine, and dopamine in the synaptic cleft to increase serotonergic, noradrenergic, and dopaminergic neurotransmission. MDMA appears to alter the conformation of the transporters, enabling monoamines to diffuse out of the neuron rather than being actively transported into the presynaptic neuron. MDMA was found to compete with monoamines for sites on the VMAT2, suggesting MDMA also promotes active release of monoamines from vesicular stores, in addition to inhibiting reuptake. MDMA extends the presence of monoamines in the synaptic cleft by inhibiting MAO-A, an enzyme that breaks down monoamines in the synapse. MDMA has self-limiting subjective and physiological effects. MDMA administration is contraindicated in with MAOI medications. Fatalities have been reported after the combination of MAOIs and MDMA in Ecstasy users. Co-administration with an SSRI may eliminate or greatly attenuate the effects of MDMA, and these medications should be tapered in line with the investigator's clinical judgment and an approved study protocol.

MDMA has been shown to acutely decrease activity in the left amygdala and increase blood flow to the PFC in the human brain. The chief mechanism behind its therapeutic effects is likely to be serotonergic, along with some norepinephrine and to a minor extent dopamine-mediated effect. Indirect, but potentially significant effects of MDMA include the release of the hormones cortisol, oxytocin, prolactin, and AVP. MDMA likely stimulates secretion of oxytocin into peripheral blood via indirect activation of $5HT_{1A}$, $5HT_{2C}$, and $5HT_4$ receptor subtypes, as well as AVP secretion via activation of $5HT_{2C}$, $5HT_4$, and $5HT_7$ receptor subtypes. Both oxytocin and AVP are implicated in the widespread regulation of behavioral aspects of mood and act on different target organs to modulate physiological functions in the body. Taken together, MDMA has a diverse array of pharmacodynamic effects in animals and humans.

6.2 Toxicology

The toxicity of MDMA has been investigated in numerous animal and *in vitro* studies published in peer-reviewed journals. Intravenous MDMA doses that cause lethality in 50% of the cases, known as the LD50, are 97 mg/kg in mice, 49 mg/kg in rats, 14 to 18 mg/kg in dogs, and 22 mg/kg in monkeys. LD50 varies between different strains of the same animal species, across the sexes, housing conditions, environmental conditions, social interactions with cohabiting animals, exercise levels, and water supply. Most preclinical toxicology data is derived from repeated dose studies. Preclinical researchers typically selected doses through use of interspecies scaling, a method of modeling human-equivalent doses in other species, however pharmacokinetic and pharmacodynamic data show this conversion is not appropriate for MDMA. As a result, most research in rodents and primates used doses of MDMA much higher than those consumed by humans, thus translation to human recreational and therapeutic use is limited. Many published epidemiological studies of Ecstasy effects in humans are also subject to the limitations in interpretation due to unknown purity, dose, and quantity of MDMA existing in Ecstasy tablets used in naturalistic settings.

Extensive preclinical toxicological studies report that high or repeated doses of MDMA can increase locomotor activity and signs of serotonin syndrome, which can damage serotonergic axons originating in the brainstem dorsal raphe nuclei, likely through oxidative stress, and this damage is associated with decreases in serotonin production, serotonin metabolites, and SERT site densities. While these findings are consistent across studies, studies in low to moderate Ecstasy users do not report an increase in a biological marker of neuronal injury, and only one of three studies in heavy users detected this marker. Retrospective studies in Ecstasy users have found contradictory effects on visual and verbal memory, planning and making decisions, and some types of visual processing. An uncontrolled prospective study of moderate Ecstasy users failed to find changes in SERT sites or signs of neuronal injury; slight changes in cerebral blood flow in the dorsolateral PFC were found. In the same study, Ecstasy users showed less improvement on a memory task than non-users. Taken together, these findings suggest possible indications of cumulative toxicity in chronic high dose dosing regimens but not as administered in clinical trials.

MDMA has not been demonstrated to be genotoxic. Consistent with this, despite very high doses of MDMA being tested in preclinical studies, none have reported carcinogenic effects. Risks posed to pregnant women by MDMA are not known. Two of three studies of Ecstasy users suggest that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth, delays in mental and motor development, but not language or emotional development. Rodent fertility, reproductive, and developmental toxicity studies with MDMA have generally found no abnormalities in gestational duration, neonatal birth weights, or physical appearance when exposure occurs during organogenesis through lactation. However, one study of fertility and developmental toxicity in mice found evidence of toxicity at doses 5 mg/kg s.c. and above when exposure occurred in both genders of a breeding pair at some point between spermatogenesis/ovulation through closure of the hard palate. The results of several behavioral tests indicate that developmental MDMA exposure combined with adult exposure in rats may interfere with some aspects of learning, including visual-spatial memory, and time spent with a novel object. MDMA exposure *in utero* exacerbated hyperthermic response to a subsequent dose to MDMA. A study in neonatal rats suggests two distinct critical periods wherein repeated MDMA doses affected learning versus acoustic startle. In conclusion, MDMA might possess weak reproductive or developmental toxicity with a daily toxic chronic dosing regimen, in contrast to six or less exposures, spaced 1 month apart, tested in clinical trials. All sponsor-supported trials of MDMA exclude pregnant and lactating people, and people who are able to become pregnant must have a negative pregnancy screen before undergoing each experimental

session and must agree to use birth control during the period of the protocol. If any subject becomes pregnant during study participation, the sponsor and clinical investigator will follow the pregnancy to outcome.

There are reports of morbidity and mortality in individuals who use Ecstasy (material represented as containing MDMA, as defined above) around the world in unsupervised and uncontrolled settings, usually involving poly-drug use (See Table 2 in Section 4.5). These events are relatively rare given the prevalence of Ecstasy use, estimated to be in the millions worldwide. The most common adverse effects in Ecstasy and poly-drug use include hyperthermia, psychiatric problems, hepatotoxicity secondary to hyperthermia, and hyponatremia (see Section 4.4 Toxicology in Animals and Epidemiological Settings and 4.5 Serious Reports, Morbidity, and Mortality in Epidemiological Settings). Published reports examining emergency department admission after ecstasy use cite anxiety and panic reactions as the most frequent reason for admission. Fatal dysrhythmias have been reported following heavy MDMA use, resulting in ventricular fibrillation and asystole. Individuals with underlying cardiac and/or pulmonary disease and preexisting conditions such as Wolff-Parkinson-White syndrome are especially at risk for heart failure and fatal arrhythmias when using MDMA. Set and setting likely play a role in the development of some Ecstasy-related adverse reports, such as vigorous exercise, lack of attention to somatic cues, and too little or too much hydration combined with pharmacological action on AVP, resulting in hyperthermia or hyponatremia. Even if ambient temperature does less to moderate the effects of MDMA on body temperature than originally believed based on animal studies, other environmental and behavioral factors, as those related to vigorous exercise, may be involved. Overall, the risks of serious reports appear to be minimal in controlled settings with adequate screening according to eligibility criteria defined in study protocols. None of these events have occurred within the context of human clinical studies with MDMA, likely due to careful screening for pre-existing risk factors and limited exposure in a controlled clinical setting.

6.3 Physiological Effects

MDMA is responsible for a series of dose dependent physiological effects due to enhanced neurochemical release of serotonin, norepinephrine, and dopamine, and for indirect effects on hormone secretion, including oxytocin and AVP, which act on different target organs to modulate physiological functions in the body. Active doses of MDMA (75 mg to 150 mg), alone or followed by a supplemental half-dose 1.5 to 2.5 hours later, are expected to produce statistically significant but transient, self-limited increases in blood pressure, heart rate, and body temperature that are likely to be well tolerated by healthy individuals. The elevation of blood pressure and increased heart rate produced by MDMA, like that produced by other sympathomimetic drugs, can lead to additional complications in people with pre-existing medical conditions that increase risk. In combination with clinical signs and symptoms, elevations in pulse and blood pressure can also lead to cardiac events, such as arrhythmias. No clinical studies have reported clinically important changes in physiological parameters.

Participants enrolled in controlled Phase 1 single dose MDMA trials conducted without sponsor support had elevations above a pre-determined cut-off of at least 140/90 mmHg (approximately 5% per trial). All participants in a subsequent trial in a separate sample given a regimen of 50 mg followed by 100 mg 2 hours later had blood pressure elevations above 140/90 mmHg. Based on the literature, effects of the initial dose of MDMA on blood pressure and heart rate are expected to have a linear dose-response relationship, and the supplemental dose may have an effect on SBP elevation. SBP above 160 mmHg was detected in 32% of blinded experimental sessions where MDMA was administered at any dose in studies of PTSD, 0% of participants on the autism spectrum, and 75% of participants that received 125 mg (blinded) with a life-threatening illness. Most of these instances occurred with the 125 mg MDMA dose group. Both peak and longest

duration of blood pressure elevation were also observed in the 125 mg MDMA group. Maximum SBP observed across studies was 200 mmHg after a 125 mg dose. MDMA doses of 40 mg and greater were associated with SBP above 160 mmHg for some people, supporting a dose dependent effect of MDMA on blood pressure. DBP above 110 mmHg was observed in 7% and 37.5% of participants after 75 mg or 125 mg blinded MDMA in participants with PTSD or a life-threatening illness, respectively. All except one of these instances occurred with the 125 mg MDMA dose. After any MDMA dose, heart rate above 110 bpm was detected in 38% of participants with PTSD, 33.3% of participants on the autism spectrum with social anxiety, and 37.5% of participants with anxiety associated with life-threatening illness. Both highest peak and maximum duration above 110 bpm were observed in 125 mg MDMA sessions. A comparison of participants receiving the supplemental dose to those who only received the initial dose in MP-1 indicate that the supplemental dose did not cause further elevation in blood pressure and heart rate beyond the initial dose.

Candidates with controlled hypertension are excluded from participation in all but one of sponsor-supported studies to limit cardiovascular risk during treatments. In MP-8, the only study that did enroll a sub-group of participants with controlled hypertension, SBP above 160 mmHg was detected in 75% (3 of 4) of participants and 67% (8 of 12) of experimental sessions where MDMA was administered to this sub-group. The prevalence of these elevations appears higher in this sub-group than the overall sample, although the prevalence could decrease in a larger group. Pre-drug SBP was typically higher in this sub-group, and peak SBP of these participants was typically at the upper end of the range of the overall sample. Final SBP readings remained 8 mmHg higher than pre-drug SBP readings in one subject that received 75 mg MDMA. The single subject with extended duration of SBP elevation had a medical history of both hypertension and hyperlipidemia. The same subject had DBP above 110 mmHg in each experimental session, suggesting that pre-existing cardiovascular risk factors beyond hypertension itself may be associated with further elevations in blood pressure, though a larger sample would be needed to establish this. None of the participants with controlled hypertension experienced AEs of the cardiovascular system.

Literature on epidemiological studies suggest a relationship between Ecstasy dose and likelihood of hyperthermia. Hyperthermia has occurred in people using Ecstasy in unsupervised and non-medical conditions, and though rare, is one of the most frequently reported serious adverse reports occurring in Ecstasy users. Environmental and behavioral factors, as well as thyroid dysregulation, may contribute to case reports and preclinical findings of hyperthermia. Findings from previous Phase 1 trials indicate that MDMA administered in a controlled setting produces a statistically but not clinically significant increase in body temperature (mean elevation of 0.6°C). The supplemental dose may limit elevations in body temperature, since it inhibits metabolism of MDMA to its bioactive metabolite MDA. MDA levels have been demonstrated to correlate with elevation in temperature in rodents. Unlike rodents, ambient temperature does not affect elevation in core temperature in humans. Controlled clinical settings have been sufficient to manage body temperature in humans.

Body temperature greater than 1°C above baseline was detected after any dose of MDMA, in 44% of participants with PTSD, with most of these cases observed in sessions with 125 mg MDMA. In individuals with autism or a life-threatening illness, 29% and 50% of subject respectively exhibited elevated body temperature after 100-125 mg MDMA (blinded). In contrast, in 20% of participants that were administered inactive placebo had an elevation of body temperature above cut-off in PTSD studies. Both peak and longest duration of body temperature elevation were observed in the 125 mg MDMA group. Across all indications, the maximum peak was 38.7°C. Vital signs in sponsor-supported Phase 2 studies presented above suggest a dose-dependent action on SBP and pulse, which is consistent with the literature on healthy volunteers.

Body temperature and DBP do not appear to be strongly related to MDMA dose. No participants receiving MDMA in sponsor-supported clinical trials have required any clinical interventions for elevated vital signs, as all values returned to normal as the effects of MDMA diminish.

6.3.1 Immunological Effects

Humans exhibit transient immunological changes after a dose of 100 mg, including reduced numbers of CD4 cells, increased numbers of NK cells, and an increase in levels of immunosuppressive and anti-inflammatory cytokines compared with levels of pro-inflammatory and immunostimulating cytokines. In several respects, these effects are similar to those that occur with other psychoactive substances, so are not unique to MDMA. Immunological effects last for approximately 24 hours after administration, and most arise indirectly from serotonin release. The significance of these immunological effects remains unclear. Previous reports did not show increases in infections after MDMA and an examination of pooled adverse events indicates that upper respiratory infection was reported in more people receiving full dose MDMA than placebo, in PTSD studies, but with upper respiratory infection occurring more often after placebo in the study of social anxiety in people on the autism spectrum. Based on results from trials conducted by the sponsor, the impact of these effects is expected to be modest. The investigators may exclude participants that might face additional risks from immunosuppression.

6.3.2 Hepatic Effects

Phase 1 studies conducted outside of sponsor support involving administration of MDMA to healthy volunteers have not reported any results of liver function after MDMA administration, and a recent published examination of safety data in a pooled sample of healthy participants found no changes in hepatic function assessed via standard liver panel. There have been no reported adverse effects on the liver from these studies. The first two sponsor-supported Phase 2 studies (MP-1, MP-2) assessed liver function after completion of two or three blinded experimental sessions. No clinically or statistically significant changes in liver function occurred in MP-1. Values for laboratory tests were within the normal range in MP-1. No AEs related to liver function have been reported in subsequent sponsor-supported studies. Only two participants in the MP-2 study reported two clinically significant hepatic abnormalities, with one likely due to hereditary factors and the other indicating inflammation in a subject with a medical history of breast cancer 3 months after the last administration of MDMA as an AE unrelated to the study drug.

6.4 Suicidal Ideation, Behavior, and Depression

There is high incidence of suicidal ideation and behavior in populations of people with PTSD, especially those suffering from chronic, treatment resistant PTSD. To determine if suicidal ideation and behavior worsens or improves after treatment in MAPS-sponsored trials, the C-SSRS is administered repeatedly throughout the study. Due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event in order to reprocess the memory in a new, therapeutic way, thoughts of ending one's life may surface during this process. However, evidence from ongoing studies indicates that these thoughts are most often transient, returning to baseline, or even improving during the acute period following MDMA treatment. C-SSRS scores have escalated during the preparatory sessions (before any drug administration), which is thought to be a result of preparatory discussion of traumatic experiences, and/or of participants tapering off long-prescribed medications, such as SSRIs and benzodiazepines. Withdrawal of these drugs is known induce suicidal ideation or behavior in some people. During both non-drug and MDMA-assisted psychotherapy sessions, participants are asked to think about and discuss their experiences, thoughts, and emotions related

to their condition. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with psychotherapy, the distress associated with psychotherapy is unavoidable, and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.

Overall the incidence of serious suicidal ideation or behavior in sponsor-supported studies is low, occurring in only a few participants post-MDMA treatment, and returning to lower scores while participants are closely monitored. As of 12 June 2019, three cases of suicidal ideation and four cases of suicidal behavior that were deemed serious across sponsor-supported Phase 2 and Phase 3 studies. Given that people suffering from severe PTSD are known to experience suicidal ideation and behavior, it is difficult to identify a single cause of the increase in suicidal thinking or behavior (i.e. exacerbation of PTSD symptoms related to medication withdrawal or to the psychotherapeutic process, or from MDMA effects). A large percentage of people enrolled in the studies reported suicidal ideation and behavior during sometime in their lives prior to study enrollment, which may reflect a manifestation of PTSD or co-morbid affective disorders. There were no reports of positive suicidal ideation or behavior after the first experimental session in participants with a life-threatening illness and only few incidences, none serious, of positive ideation in adults on the autism spectrum during the study. When positive serious ideation or behavior occurred after study enrollment, the investigators made follow-up observations of C-SSRS to ensure subject safety and tracked scores until they returned to non-serious levels.

During Screening, throughout MDMA-assisted psychotherapy, and during assessment of study measures, participants are asked to think about and discuss their thoughts and emotions relating to the traumatic event or events. They may experience intense emotional responses or suicidal ideation as a result of recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing the trauma, symptoms related to the trauma or the effects of PTSD on life function can produce distress and exacerbate suicidal ideation during and immediately after psychotherapy sessions. Psychotherapy is conducted as part of these studies, and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable. Therapy teams provide emotional support to participants during any psychological distress during these studies.

Therapy teams minimize risks by carefully evaluating all participants to determine if there is a current risk of suicidal behavior. Participants with a history of suicide attempts are not excluded unless significant risk of suicidal behavior is present at the time of Screening. Participants are enrolled according to the Eligibility Criteria based on the clinical judgment of the site physician, therapy team, and Medical Monitor.

6.5 Adverse Events

Overall, adverse effects of MDMA are modest and generally have not been associated with serious discomfort in healthy volunteers or in people in MAPS Phase 2 studies. Risks posed by sympathomimetic effects of MDMA treatments are addressed in MAPS' clinical trials by excluding people with pre-existing cardiovascular disease, cerebrovascular disease or uncontrolled hypertension, and by monitoring blood pressure, body temperature, and pulse. Common reactions reported in clinical trials are transient and diminish as drug effects wane during the MDMA session and over the next 24 hours. Once the drug leaves the body, three to four days post-treatment, most reactions diminish. Reactions are monitored daily for 1 week after each treatment and followed until resolution. The most common acute reactions at any severity after 125 mg MDMA were tight jaw, lack of appetite, dizziness, and nausea; and reactions related to thermoregulatory and osmoregulatory effects MDMA that occurred at a higher rate than

placebo were sensitivity to cold, perspiration, dry mouth, and thirst. Tight or clenched jaw, perspiration, headache and lack of appetite were most commonly reported after MDMA versus placebo in the study of anxiety in response to a life-threatening illness, and lack of appetite, difficulty concentrating and muscle tension were most commonly reported in the study of social anxiety in people on the autism spectrum. Other reactions, including anxiety, headache, fatigue, low mood, and insomnia, were reported at the same or higher frequency in the placebo group vs. 125 mg MDMA group in the PTSD sample. Anxiety was the most commonly reported across MDMA and placebo/comparator groups and could be related to MDMA or PTSD symptoms.

During the week after each experimental session, the most commonly reported reactions at any severity in the active dose MDMA groups across studies, with PTSD studies overrepresented. Of these reactions, only decreased appetite and need more sleep were appreciably elevated above the placebo/comparator group. Severe AEs after active dose MDMA, although not necessarily related to drug, included abdominal pain, sinusitis, concussion, exposure to violent event, lower limb fracture, breast cancer stage 1, anger, anxiety, depressed mood, insomnia, major depression, obsessive rumination, and panic attack. All participants fully recovered from these events.

There have been reports of morbidity and mortality in individuals who use Ecstasy (material possibly containing MDMA) in uncontrolled settings outside of research studies, usually involving poly-drug use and moderate to intense physical activity. Individuals experiencing these adverse effects have not been carefully screened based on eligibility criteria and are likely to have pre-existing medical conditions or underlying cardiac and/or pulmonary disease that influence metabolism and disposition of MDMA in the body. These events are relatively rare given the prevalence of Ecstasy use, estimated to be in the millions worldwide. The most common adverse effects include hyperthermia, psychiatric problems, hepatotoxicity secondary to hyperthermia, and hyponatremia (see Table 2). Overall, the risks of Serious Adverse Reactions (SARs) have been addressed and constrained by limited exposure and drug administration in controlled settings with adequate screening according to eligibility criteria defined in study protocols. To date, only one SAR of exacerbation of pre-existing ventricular extrasystoles has been reported within the context of MAPS-sponsored Phase 1 or Phase 2 clinical studies. All SARs at least possibly related to MDMA and not included in Table 71 (below) should be considered unexpected and are subject to expedited reporting as Suspected Unexpected Serious Adverse Reactions (SUSARs). The table below was developed based on a survey of case reports that could be of concern in the published scientific literature on MDMA or Ecstasy.

Table 71: Reference Safety Information Based on Case Reports of Morbidity and Mortality Possibly Associated with MDMA

Body System	Adverse Reaction
Thermoregulatory Disorders (MedDRA "Body Temperature conditions" under "General Disorders and Administrative Site Conditions"	Hyperthermia, Hyperpyrexia, (leading to: Rhabdomyolysis, Hypoglycemia)
Cardiac Disorders	Cardiac valve disease (Valvular Heart Disease), Ventricular fibrillation, Cardiac arrest, Arrhythmia, Dysrhythmia, Myocardial infarction, Generalized tonic-clonic seizure, Acute coronary syndrome, Myocardial necrosis, Cardio-respiratory arrest, Cardiomyopathy
Osmoregulatory Disorders (MedDRA 17.1 "Electrolyte and fluid balance conditions" under "Metabolism and Nutrition Disorders	Syndrome of Inappropriate Antidiuretic Hormone, Urinary retention, Hyponatremia, (sequelae: Cerebral oedema, Acute renal failure
Hepatobiliary Disorders	Acute fulminant hepatitis, Liver disease, Disseminated intravascular coagulation
Injuries, Poisonings, and Procedural Complications	Anaphylactic shock, Facial rash eruption, swollen lip (allergic or mechanical injury)
Nervous System Disorders	Cerebral oedema; Hemorrhage, Infarct, Hippocampal sclerosis, Encephalopathy, Amnestic syndrome
Dental And Gingival Disorders (under "Gastrointestinal Disorders")	Xerostomia, Bruxism, Dental erosion
Psychiatric Disorders	Psychotic episode, Depressive episode
Respiratory, Thoracic, and Mediastinal Disorders	Subcutaneous Pneumomediastinum, Epidural pneumatosis, Diffuse alveolar hemorrhage, Asthma
Eye Disorders	Lagophthalmos, Keratopathy, Bilateral sixth nerve palsy

SARs related to administration of MDMA in MAPS-sponsored clinical trials have been rare and none have been life-threatening. One possibly drug-related expected SAR has occurred to date in this clinical development program. This event was an increase in frequency of ventricular extrasystoles experienced during open-label treatment with 125 mg MDMA, which resolved with full recovery to baseline after the study drug's effects ceased. The subject was hospitalized for observation and recovered fully after the event, with no cardiac damage. Excluding people with cerebrovascular or cardiovascular disease will reduce the likelihood of risks arising from the cardiovascular effects of MDMA.

6.6 Risk Assessment and Mitigation

Study procedures and eligibility criteria have been developed based on Phase 2 PTSD trials to exclude potential participants with pre-existing exclusionary medical conditions that would exacerbate risk. The therapy teams and site physicians are available via mobile phone throughout the study if any problem occurs when a participant is not at the site. In the event of a medical emergency or any other medical problem during an experimental session, the site physician will be immediately available by telephone, and based on assessment of the situation, they will make the decision to either evaluate the participant themselves at the site, or arrange for transfer of the participant to the Emergency Department.

Risk mitigation procedures are described by risk category below. Risk Categories were determined by review of possible risks within the Risk Assessment and Categorization Tool (RACT).

6.6.1 High Level Risks

High Risk does not indicate an event is more likely to happen but indicates per the RACT assessment that new and or more complex procedures are required in the study to ensure screening is adequate to eliminate or manage the risk in the patient population. No high-level risks of MDMA have been identified based on the RACT assessment.

6.6.2 Medium Level Risks

Medium Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that new or many procedures, which are not complex, are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

Cardiovascular and Cerebrovascular Risks and Mitigation

MDMA is known to transiently increase heart rate and blood pressure in a dose-dependent manner that is generally not problematic for physically healthy individuals. These changes should last no more than 8 hours. Participants with PTSD in MAPS-sponsored Phase 2 studies do not appear to differ from healthy individuals in this sympathomimetic, physiological response. Most people do not experience elevations in cardiovascular parameters that exceed those seen after moderate exercise. An examination of safety data drawn from Phase 2 studies of MDMA-assisted psychotherapy detected a dose-dependent increase in SBP but not DBP. Characterization of sympathomimetic effects among participants with controlled hypertension is ongoing.

Risks posed by elevated blood pressure will be addressed by excluding people with pre-existing uncontrolled hypertension and monitoring blood pressure and pulse, as described in study protocols. Before and after drug administration in Experimental Sessions, the therapy teams monitor vital signs. The therapy teams attend to clinical signs and symptoms during Experimental Sessions, such as chest pain, shortness of breath, neurological deficit or confusion other potential indicators of end organ effects of hypertension that prompt additional vital sign measurements and intervene if appropriate. Therapy teams notify the site physician if this occurs for evaluation. If any participant has neurological deficits, as assessed by the site physician, whether they are associated with hypertensive crisis, they will be monitored as described above, for rare complications of cardiovascular effects, such as stroke or acute myocardial infarction (AMI). If a participant experiences ischemic type chest pain, whether it is associated with hypertensive crisis, they are given 0.4 mg of sublingual nitroglycerin every 5 minutes as needed for chest pain pending transport to the hospital. If evaluation at the hospital reveals a nonhemorrhagic stroke, there will be enough time to administer recombinant tissue plasminogen within the 3-hour time frame recommended in the American Academy of Neurology/American Heart Association guidelines [729].

If further evaluation at the hospital reveals that the participant has had an AMI, they will be well within the time frame required for definitive therapy. The American College of Cardiology/American Heart Association guidelines for the treatment of AMI recommend percutaneous transluminal coronary angioplasty (PTCA) as the treatment of choice when it can be performed within 90 minutes of arrival at the hospital in patients who present within 12 hours of an episode of chest pain lasting more than 30 minutes and who have ECG evidence of AMI [730]. Any participant who experiences such medical complications during an Experimental Session will not be given another Experimental Session, unless it is approved by the investigator, site physician, and the Medical Monitor.

As the characterization of QT effects for the API is ongoing, QT interval may be evaluated in the event of hospitalization for management of cardiovascular or cerebrovascular event. If at any time a participant develops a QT/QTc interval >500 ms or of >60 ms over Baseline during ECG evaluation, the participant will be discontinued from treatment.

Psychological Risks and Mitigation

Mild anxiety and depressed mood are occasionally reported 1 to 3 days after MDMA administration [10, 11]. Psychological distress from MDMA could arise from the first indications of MDMA effects until the last effects have dissipated or even later. Anxiety or distress during the session may last for as little as 5 minutes or for as long as 5 hours or more. In addition, psychological distress could arise following an Experimental Session as a result of participants having difficulty integrating their experience after the MDMA effect has subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been self-limiting and have responded well to reassurance from the therapy team, with occasional use of benzodiazepines for anxiety. In this study, participants will have the intention of confronting and working through traumatic experiences. Accordingly, signs of psychological distress, panic, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process.

Proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute reactions. The potential for destabilizing psychological distress will be minimized by:

- Excluding people who might be more vulnerable to it (such as people diagnosed with bipolar affective disorder type 1 or with psychotic disorders)
- Preparatory Sessions of non-drug psychotherapy before the Experimental Session
- Creating an atmosphere of trust during the Experimental Session
- Close monitoring
- Phone contact with participants during the week after the Experimental Session
- Integrative Sessions
- Overnight stays at the study site for the night of each Experimental Session for PTSD studies. Qualified personnel will be available during the overnight stay to respond to the needs of the participant. Attendants will be instructed to contact the therapy team upon request or at the appearance of signs of a potential SAE.

During the Preparatory Sessions, participants will be made aware of the fact that difficult emotions, including grief, rage, fear, or panic, may arise during Experimental Sessions. Every effort will be made to help participants resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the Experimental Session, including empathic listening on the part of the therapy team and performance of diaphragmatic breathing by participants.

If the participant is severely agitated, anxious, in danger of self-harm or suicide, or is experiencing any other severe psychological distress, at the end of a psychotherapy session, at least one member of the therapy team remains with the participant for at least 2 more hours. During this time, the therapy team employs affect management techniques, talks with the participant to help them gain cognitive perspective of their experiences, and helps the participant implement the self-soothing and stress inoculation techniques presented during the Preparatory Sessions. If the participant remains severely anxious, agitated, in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of the 2-hour stabilization period, the site physician and therapy team decide between the following options:

1. If severe distress occurs at the end of an Experimental Session, a psychiatric nurse, therapeutic assistant, physician, or therapy team member would stay with the participant until the severe distress resolves or until the time of their Integrative Session appointment the following morning. The therapy team would then meet with the participant daily until the period of destabilization has passed.
2. If the participant experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an Experimental Session, a licensed therapy team member or the site physician may prescribe a benzodiazepine (specifically, lorazepam) and/or sleep aid (e.g., zolpidem). The site physician should not prescribe an SSRI, SNRI, or monoamine oxidase inhibitor (MAOI) in this context, unless it has been determined that the participant will be withdrawn from the study. Residual symptoms would be addressed during the frequent follow-up psychotherapy visits with the therapy team.
3. If a participant should become psychotic, arrangements would be made to stabilize them or transfer them to the ED if hospitalization is necessary. If any participant is hospitalized after a severe psychological reaction they would be suspended from the protocol until after recovery or stabilization, at which time the investigator and/or site physician would carefully evaluate the participant's emotional status.

For those participants engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the participant's outside therapist(s) would be involved in the management of any psychiatric complications. For those participants engaged in an ongoing psychotherapeutic relationship with the investigator or member of the therapy team, the management of any psychiatric complications will be undertaken by them in their capacity as the participant's therapist.

6.6.3 Low Level Risks

Low Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no new or complex procedures are needed to ensure screening is adequate to eliminate or manage the risk in the patient population.

Thermoregulatory Risks and Mitigation

MDMA administered in a controlled setting produces only a slight increase in body temperature [11]. Ambient temperature does not enhance or attenuate this slight elevation in humans. In data gathered from sponsor-supported Phase 2 studies, it was found that compared to placebo, a higher percentage of participants receiving MDMA had peak body temperatures greater than 1 degree Celsius (° C) above Baseline. However, there was no strong relationship between dose of MDMA and peak body temperature or between MDMA dose and elevation above threshold of 1° C above Baseline.

Ambient temperature should be kept at a comfortable level during Experimental Sessions. If temperature rises more than 1° C or the participant states that they feel hot, attempts should be made to decrease body temperature and increase comfort by removing blankets and layers of clothing, decreasing the ambient temperature, and, if necessary, directing a fan toward the participant. If at any time the temperature rises more than 1.5° C above Baseline despite these efforts, the site physician should be consulted for further evaluation and treatment.

Osmoregulatory Risk and Mitigation

MDMA administered in a controlled setting is not expected to have any risks of osmoregulatory changes. Participants are not allowed to drink more than three liters of electrolyte-containing fluids over the course of the Experimental Session and fluid intake is spread out appropriately during the session. If a participant exhibits any signs of toxicity or clinically significant dilutional hyponatremia despite these precautions after an Experimental Session, they would not receive another Experimental Session unless it is approved by the investigator, site physician, and the Medical Monitor.

Genotoxicity Risk and Mitigation

To reduce the risk of metabolic activation and formation of nitroso-derivatives of MDMA due to interactions with nitrates or nitrites in food, participants are required to have fasted (no intake other than alcohol-free liquids) for 10 hours prior to drug administration in Experimental Sessions.

Reproductive and Developmental Risks and Mitigation

Risks posed by MDMA to pregnant people are not known. One of two studies of Ecstasy users suggest that use of Ecstasy and other drugs during pregnancy may be associated with some abnormalities at birth while the other failed to find this association [399, 400].

Pregnant and lactating people will be excluded from participation in the study. Participants who are able to become pregnant must have a negative pregnancy screen before undergoing each Experimental Session and must agree to use adequate birth control for the duration of the study during the Treatment Period. Procedures have been put in place to mitigate risk of reproductive or developmental exposure to MDMA.

6.6.4 Minimal Risks

Minimum Level Risk does not indicate the likelihood the event will occur but indicates per the RACT assessment that no procedures are needed beyond basic monitoring to ensure screening is adequate to eliminate or manage the risk in the patient population.

Common Expected AEs

Common expected AEs are typically observed during Experimental Sessions but are transient and diminish as MDMA is metabolized and excreted over the next 72 hours after dosing. Common AEs most frequently reported in people after MDMA versus placebo during Experimental Sessions include muscle tightness in the jaw, lack of appetite, fatigue, dizziness, and nausea. Anxiety was the most highly reported reactions during experimental sessions after active dose MDMA but also after inactive placebo. During the week following treatment, common reactions included headache, insomnia, lack of appetite, low mood, muscle tightness in the jaw, nausea, need for more sleep, and restlessness may be reported, and weakness was more common after MDMA than placebo during this period though not frequently reported overall. Severe anxiety, insomnia, fatigue, and depressed mood are commonly reported in PTSD studies in both placebo and MDMA groups. Common AEs are typically self-limiting. Elevations in anxiety and poor sleep respond to management with short-acting low dose benzodiazepines (specifically, lorazepam) or sleep aids as needed, per clinical judgment of the site physician.

Potential Neurotoxicity Associated with Ecstasy Use

Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials [731]. However, these claims are based on studies that employed inappropriately high doses of MDMA utilized in animal studies and on human studies comparing the effects of repeated use of Ecstasy, often along with other drugs. Meanwhile, another recently published meta-analysis has taken careful steps to overcome methodological limitations in previous work and found only modest evidence of neurotoxicity [61]. The sponsor has carefully considered the risks of such neurotoxicity and concludes that they are minimal in the proposed study. This conclusion is supported by empirical and toxicokinetic evidence and is consistent with the lack of toxicity reported in previous clinical MDMA studies. It does not appear that MDMA-assisted psychotherapy negatively impacts cognitive function.

Abuse Potential

Despite its classification as a Schedule I drug, an examination of findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants, such as cocaine or methamphetamine. Studies assessing prevalence of problematic Ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop problematic Ecstasy use or dependence. Across MAPS-sponsored studies of MDMA-assisted psychotherapy for people with PTSD, 8 of 92 participants reported using Ecstasy subsequent to study participation, with 6 of the 8 participants having used Ecstasy prior to study enrollment. Several participants volunteered that they would not seek out Ecstasy outside of a psychotherapeutic setting. Diversion is not an issue for sponsor-supported studies because MDMA will only be administered under the supervision of the clinical investigator and no take-home doses are permitted. MDMA is handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

7.0 Reference Safety Information for Regulatory Reporting

The Reference Safety Information (RSI) below outlines expected Serious Adverse Reactions (SARs) for regulatory reporting purposes in the European Economic Area (EEA) region and the information within the RSI does not present a comprehensive overview of the safety profile of the investigational medicinal product (IMP).

Table 72: Serious Adverse Reactions for the IMP Considered Expected for Safety Reporting Purposes in EEA Region

System Organ Class	SARs	As of May 31, 2019 : Number of subjects exposed within the development program (N) = 267 Number of subjects exposed outside the development program (N) = 1570		
		All SARs	Occurrence of fatal SARs	Occurrence of life-threatening SARs
		N* (%)	N (%)	N (%)
None	None	0 (0.0)	0 (0.0)	0 (0.0)

* N= number of subjects who have experienced the SAR

No SARs are considered expected by the sponsor for the purpose of expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) and identification of SUSARs in the "Cumulative summary tabulation of serious adverse reactions" in the Development Safety Update Report (DSUR) for the IMP. Although one SAR has been observed to date in MAPS-sponsored clinical trials, it has not been observed more than once and hence does not meet the definition of an SAR for the RSI.

8.0 Conclusion

Based on the current state of scientific knowledge, the risk for subjects meeting criteria for clinical studies who are exposed to MDMA at the single intermittent dosing schedule used in sponsor-supported studies appears to be low. The overall rates of AEs and reactions across phase 2 studies are low and the reactions and AEs are self-limiting. Many of the AEs and expected reactions reported in the studies are likely related to background events representing the underlying illness being treated, or the expected result of psychotherapy addressing traumatic experiences.

Future studies conducted by the sponsor are intended to further develop the safety profile of MDMA in the PTSD subject population, and subjects with other indications. The sponsor is exploring the use of MDMA-assisted psychotherapy in the treatment of anxiety, including social anxiety in people on the autistic spectrum and anxiety resulting from a life-threatening illness. MDMA-assisted psychotherapy appears to be a promising treatment method for chronic PTSD. More clinical trials in larger subject populations are warranted. It is hoped that MDMA, with its unique pharmacological mechanisms combined with a novel mode of administration in conjunction with psychotherapy, can improve upon first line PTSD and anxiety treatments in terms of side effect profiles, efficacy and duration of effect.

9.0 Appendix

Table 73: Highlights of ±3,4-methylenedioxymethamphetamine (MDMA) Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Maximum proposed clinical dosing regimen: Three divided single-dose exposures spaced approximately a month apart of 80mg -120 mg initial dose MDMA and 40mg- 60 mg supplemental half-dose MDMA, administered 1.5 to 2 hours after initial dose. Mean (%CV) C_{max} and AUC at the single maximum proposed clinical dose 125 mg MDMA [675]: C_{max}: 223.5 ± 38.5 ng/mL (N=136) AUC: 948 ± 172.9 ng*h/mL (N=136) Mean (%CV) C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen: Clinical dosing regimen does not reach steady state, single-dose only with at least two weeks washout between doses	
Maximum tolerated dose	NOAEL: 100 mg/kg in rat	
Maximum dose tested	Single Dose	150 mg
	Multiple Dose	The drug is designed to be given as a divided single-dose on Day 1: Initial dose followed by supplemental half-dose given 1.5-2.0 hours later. On Day 30 and Day 60, additional single-doses on the same schedule may be given if warranted.
Exposures Achieved at Maximum Tested Dose	Single Dose	Initial dose 150 mg (N=2) [14]: MDMA C_{max}: 441.9-486.9 ng/mL AUC_{0-24}: 5132.8-5232.0 ng*h/mL MDA C_{max}: 34.2-31.4 ng/mL AUC_{0-24}: 373.9-590.0 ng*h/mL
	Multiple Dose	Initial dose 50mg + Supplemental dose 100 mg, 2.0 hours later (N=10) [375]: MDMA C_{max} +12.8%, AUC_{∞} +16.2% MDA C_{max}: +25%, AUC_{∞} +37.5% HMMA C_{max} -38.2%, AUC_{∞} -29.8%
Range of linear PK* **More PK data was available for 75 mg dose (N=8), which was used as basis for dose*	MDMA C_{max} normalized to 75mg 100 mg (N=2): 1.53 125 mg (N=8): 1.81** 150 mg (N=2): 3.55 MDA C_{max} normalized to 75 mg	MDMA AUC_{0-24} normalized to 75 mg 100 mg (N=2): 1.39 125 mg (N=8): 1.97 150 mg (N=2): 3.89 MDA AUC_{0-24} normalized to 75 mg 100 mg (N=2): 1.66 125 mg (N=8): 1.76 150 mg (N=2): 3.94

normalization [14]	100 mg (N=2): 2.35 125 mg (N=8): 1.76 150 mg (N=2): 4.21 ** This ratio was confirmed in a more recent study with N=29 receiving 75 mg MDMA [675]. 125 mg (N=110): 1.83	
Accumulation at steady state	Therapeutic use is single-dose, MDMA does not reach steady state	
Metabolites	MDMA metabolism in the liver is saturable in a dose-dependent manner and follows non-linear pharmacokinetics. MDMA is metabolized by *N*-demethylation to the only active metabolite MDA by several enzymes, including CYP2D6 (>30%), CYP1A2, CYP3A4, CYP2C19, and CYP2B6, followed by COMT. The parent compound and MDA are further *O*-demethylated to HHMA and HHA, respectively. Both HHMA and HHA are subsequently *O*-methylated mainly to HMMA and HMA. These four metabolites, particularly HMMA and HMA, are excreted in the urine as conjugated glucuronide or sulfate metabolites.	
Absorption	Absolute/Relative Bioavailability	MDMA has not been studied with I.V. administration in humans to date.
	T_{max}	T_{max} by dose of MDMA administered [14]: • Parent: 75 mg: 1.8 ± 0.4 hours 100 mg: 2 – 3 hours 125 mg: 2.4 ± 1.0 hours 150 mg: 1.5 – 2 hours • Active Metabolite MDA: 75 mg: 5.1 ± 2.6 hours 100 mg: 4 – 6 hours 125 mg: 7.1 ± 2.8 hours 150 mg: 4– 10 hours
Distribution	Vd/F or Vd	Vd/F by dose of MDMA administered [129]: 1.0 mg/kg MDMA (43-106 mg): 5.5 ± 1.1 L/kg 1.6 mg/kg MDMA (69-150 mg): 5.5 ± 1.3 L/kg
	% bound	34-40% Bound
Elimination	Route	• Primary route hepatic, 50% to 75% metabolized • Renal clearance 8% to 11% All metabolites of MDMA in urine were detected as glucuronide and sulfate conjugates. After 1.0 mg/kg MDMA, the majority was excreted in urine as the inactive metabolites HMMA sulfate (13%), followed by DHMA 3-sulfate (9%), and

		HMMA glucuronide (5%), and only 8% as the parent compound MDMA[129]. After 1.6 mg/kg MDMA, the majority was excreted in urine as the inactive metabolites HMMA sulfate (10%), followed by DHMA 3-sulfate (9%), and HMMA glucuronide (4%), and only 11% as the parent compound MDMA. Studies examining metabolism of 100 mg MDMA reported similar excretion values [129].
	Terminal $t_{½}$	Terminal $t_{1/2}$ by dose of MDMA administered [129]: • Parent MDMA: 1.0 mg/kg (43mg-106mg): 6.9 ± 3.4 h 1.6 mg/kg (69mg-150 mg): 8.1 ± 2.1 h • Active Metabolite MDA: 1.0 mg/kg (43mg-106mg): 10.6 ± 4.3 h 1.6 mg/kg (69mg-150 mg): 12.3 ± 3.7 h
	CL/F or CL	Renal CL by dose of MDMA administered [14]: 75 mg: 12.8 ± 5.6 L/h 100 mg: 20.4 – 12.3 L/h 125 mg: 13.0 ± 5.4 L/h 150 mg: 5.2 – 11.3 L/h CL/F by dose of MDMA administered [129]: 1.0 mg/kg (43mg-106mg): 0.62 ± 0.19 L/h/kg 1.6 mg/kg (69mg-150 mg): 0.48 ± 0.11 L/h/kg
Intrinsic Factors	Age	Pediatric PK will be tested after initial NDA No information is available on effect of age on exposure, but from a mechanistic point of view, the enzymes responsible for metabolism of MDMA are not known to be affected by age.
	Sex	PK parameters by dose of MDMA administered [675]: 75 mg MDMA MDMA C_{max}: Women 133 ± 27 ng/mL MDMA C_{max}: Men 116 ± 29 ng/mL MDMA AUC: Women 547 ± 127 ng*h/mL MDMA AUC: Men 493 ± 113 ng*h/mL 125 mg MDMA MDMA C_{max}: Women 252 ± 40 ng/mL MDMA C_{max}: Men 195 ± 37 ng/mL MDMA AUC: Women 1058 ± 185 ng*h/mL MDMA AUC: Men 838 ± 160 ng*h/mL
	Race	PK parameters by dose of MDMA administered [129]: 1.0 mg/kg (43mg-106mg) MDMA: MDMA C_{max}: +22% in Blacks vs. Europeans MDMA AUC: +19% in Blacks vs. Europeans MDA C_{max}: +9.3% in Blacks vs. Europeans 1.6 mg/kg (69-150 mg) MDMA: MDMA C_{max}: +21% in Blacks vs. Europeans MDMA AUC: +8% in Blacks vs. Europeans

		MDA C_{max}: +1.4% in Blacks vs. Europeans
	Hepatic & Renal Impairment	CYP2D6 poor vs. extensive metabolizers [624]: MDMA C_{max} +15% MDA C_{max} +50% HMMA C_{max} -50-70% A PK study in subjects with moderate hepatic impairment is planned concurrent with Phase 3 studies. Due to <20% renal clearance of the parent compound, a renal impairment PK study is not planned to support the initial NDA.
Extrinsic Factors	Drug interactions	Paroxetine (N=7), CYP2D6 inhibitor, metabolized by CYP2D6>>CYP3A4>CYP1A2>CYP2C19>CYP3A5 [732]. MDMA C_{max} +17% AUC_{0-27} +23% MDA C_{max} +17% AUC_{0-27} +16% Bupropion (N=16) CYP2D6 and CYP2B6 inhibitor, metabolize[639]. MDMA C_{max} +14% AUC_{0-24} +33% $t_{1/2}$ +24% MDA C_{max} -15% AUC_{0-24} -12% 30mg Dextromethorphan (N=12), metabolized by CYP2D6>> CYP3A4> CYP2B6. Co-administered with 1.5mg/kg MDMA [622]. Dextromethorphan C_{max} +87.9% AUC_{0-8} +89.1% Dextrorphan C_{max} -93.0% AUC_{0-8} -90.4% 3-methoximorphinan C_{max} +72.2% AUC_{0-8} +64.6% Hydroxymorphinan-3-ol C_{max} -87.2% AUC_{0-8} -86.7% Methylphenidate (N=16), metabolized by CYP2D6 [599]

		MDMA C_{max} -3.5% AUC_{0-24} +3.2% MDA C_{max} -3.6% AUC_{0-24} -3.4% Methylphenidate C_{max} +<0.1% AUC_{0-24} -<0.1%
	Food Effects	Will be tested concurrent with Phase 3
Expected High Clinical Exposure Scenario	Metabolism of MDMA is complex, with 50-75% of the parent compound being metabolized. Major enzymes involved in metabolism of MDMA include: CYP2D6 (>30%)> CYP1A2>CYP3A4>CYP2C19> CYP2B6. Active doses of MDMA (75 mg -125 mg) reversibly inhibit CYP2D6 and decrease CYP3A4 activity, with CYP2D6 activity normalizing after 10 days post-drug. Compensatory metabolic mechanisms have been demonstrated when CYP2D6 is inhibited, such as an increase in CYP1A2 activity by 20-40% [623]. In the therapeutic dose range of 75-125 mg, a concentration-dependent effect is observed. Studying higher doses of MDMA in healthy subjects poses both safety and ethical concerns due to the Schedule 1 controlled substance status of MDMA. Although elevation of blood pressure and heart rate has been observed, these cases have not been accompanied by clinical signs and symptoms of end organ effects of hypertension (e.g. chest pain, shortness of breath, neurological deficit or confusion) and have not been considered clinically significant AEs. The worst-case scenario would be strong inhibition of both CYP2D6, CYP2B6, and CYP1A2 combined with administration of an initial dose of 125 mg followed by a supplemental half-dose 1.5-2.0 hours later. Based on the exposure observed with CYP2D6/CYP2B6 inhibition by Bupropion with a C_{max} elevation of +14% and AUC elevation of +33%, combined with a C_{max} elevation of +12.8% and AUC elevation of +16.2% with a supplemental dose, the increase in exposure is estimated to be C_{max} +26.8% of MDMA and AUC +49.2% of MDMA. If CYP1A2 is additionally inhibited, a conservative estimate would be to double the exposure estimate for a C_{max} elevation of +53% and AUC could be elevated up to +75%. 125 mg: If an estimated 60% of metabolism is shut down, moderate hepatic impairment would double the AUC to be equivalent to 250mg MDMA. PK exposure to single-doses above 150 mg MDMA remain untested to date. PK studies planned to be conducted concurrent with Phase 3 will cover a supra-therapeutic dose of 225 mg, which is sufficient close to 250 mg MDMA. In MAPS-sponsored clinical trials, MDMA is only administered under the supervision trained and qualified healthcare professionals in a controlled clinic setting.	

Preclinical Cardiac Safety	**In vitro nonclinical data:** Langendorff perfused hearts isolated from male Sprague Dawley rats were used to explore in vitro effects of MDMA on QT interval. Solutions of MDMA (1, 3, 10 and 30 μM) were prepared by dissolving in Krebs-Henseleit buffer. After equilibration of the isolated rat heart, MDMA (1, 3, 10 and 30 μM) was added to the perfusate, with each concentration being allowed to perfuse for 15 min before being replaced with the next highest concentration. ECG and heart rate were continuously monitored using a Powerlab collation unit (Powerlab and Chart program V5, AD Instruments). Detection of P, QRS and T waves from the ECG waveform was facilitated with the Signal Averaged Electrocardiogram (SAECG) extension for Chart 5. Briefly, ECG cycles over 15-second sampling periods within each 15-min block were aligned and averaged. This ensured that random noise and signal uncorrelated with the ECG tended to cancel out, leaving the ECG components themselves unaffected. Heart rate was calculated from the R–R interval of the ECG waveform. ANOVA of the PQ, QRS interval, and T wave amplitude T(h) showed no effect of MDMA. ANOVA of the QT interval showed an effect of MDMA [$F(5,50)=5.22$, $p<0.01$]. Post-hoc comparisons did not reveal a significant effect of MDMA when compared to baseline (80 ± 9 ms), although a trend towards an increase in the QT interval was observed following application of 30 μM MDMA in vehicle-treated (100±6 ms) groups. In addition, MDMA did not influence P wave, R or ST segment heights of the ECG trace (N= 6 animals per group). Although a trend towards prolongation of the QT interval was observed with MDMA, it failed to reach significance. No increase in T wave amplitude of the ECG was observed with MDMA. These results support that the central and sympathomimetic effects of MDMA, rather than any direct action on cardiac tissue, are responsible for the sustained tachycardia observed in vivo [733]. **In vivo clinical data:** In an early clinical study [666] with 2-lead ECG monitoring during exposure to 1.5 mg/kg (71mg-167mg) MDMA, the mean change in QTc upon MDMA dosing relative to placebo was about 4.41 ms with an upper 95% confidence limit of 10.47 ms. The experimental design including the sample size, timing of the ECG measurements and type of ECG may not be optimal for precise assessment of QTc change. However, these data do support that the change in QTc, if any, is small and clinically unimportant. Despite a small sample size of N=24, the upper confidence limit is barely 10 msec. With more samples and 12-lead ECG, the upper confidence limit would likely be much less than 10 msec. See Type A Meeting Submission dated April 4, 2017 for methodology and individual data.
Clinical Cardiac Safety[a]	**11 sponsored Phase 2 studies in patients (N=150)**, doses ranging from 25 mg, 30mg, 40mg, 75 mg, 80 mg, 100 mg, 120 mg, 125 mg, to 150 mg MDMA with supplemental half-dose 1.5-2 hours after initial dose. Participants randomized to 25-75 mg MDMA group had cross over to active dose (100 -125 mg MDMA). Number of exposures: 1 to 6 single-dose experimental sessions (1-3 blinded, 2-3 open-label exposures). **2 sponsored Phase 1 studies in healthy volunteers (N=83)**, doses ranging from 100 mg to 125 mg MDMA with supplemental dose 1.5-2 hours after initial dose. Number of exposures: 1 to 2 single-dose experimental sessions

	56 investigator-initiated Phase 1 studies (N=1130), doses ranging from 0.25 mg/kg to 3.1 mg/kg MDMA (17.5-217 mg based on 70 kg standard weight assumption). Number of exposures: At least 1. **The following cardiac safety events have been observed** in the MDMA group in Phase 2 clinical trials to date, none were observed in placebo and none were severe. Adverse events resolved without treatment. Furthermore, no QT-related symptoms or signs were observed in the patient trials thus far. *Syncope* 1 blinded PTSD subjects receiving active dose MDMA had this AE. Three subjects had a history of syncope prior to exposure, but only 1 of 3 experienced the AE. Reported 2 months post second exposure, duration 1 day. *Exacerbation of ventricular extrasystoles* 1 blinded PTSD subjects receiving active dose MDMA had this AE. Subject had one PVC at baseline EKG prior to exposure and a history of PVCs. Observed during fifth exposure, duration 1 day, reported to sponsor as expected SAR based on hospitalization for observation and further assessment. *Sinus tachycardia* 1 blinded PTSD subjects receiving active dose MDMA had this AE. Reported 12 days post second exposure, duration 54 days. Subject saw treating physician for a Holter monitor during this period. Concomitant Adderall prescription ended prior to this AE. *Palpitations* 1 blinded PTSD subjects receiving active dose MDMA had this AE. Observed during fourth exposure, duration 1 day. **In the Phase 2 study MP-8, subjects with controlled hypertension** (kept normal with medication) were allowed entry into the study if they passed a nuclear stress test and carotid ultrasound in addition to normal EKG at screening. A total of 4 controlled hypertension subjects were enrolled and treated (30 mg N=1, 75 mg N=1, 125 mg N=2). Subjects receiving 75 mg and 125 mg experienced Systolic Blood Pressure above 160 mmHg during both blinded exposures to MDMA but did not experience any cardiac AEs. Peak SBP during exposure was 131 mmHg with 30 mg MDMA, 179 mmHg with 75 mg MDMA and 177 mmHg with 125 mg MDMA. During the open-label crossover with 100-125 mg MDMA, the peak SBP during exposure was 193 mmHg. The sponsor is continuing to enroll this sub-group in Phase 3 studies to further explore associated risk factors.

[a] Samples size specified are as of the version date of this document in order to provide the most up to date information available.

10.0 References

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