INVESTIGATOR'S BROCHURE

SPONSOR: Multidisciplinary Association for Psychedelic Studies

PRODUCT: 3,4-methylenedioxymethamphetamine (MDMA)

IND #: 63,384

EDITION: 7th Edition

RELEASE DATE: August 1, 2013

REPLACES: 6th Edition, dated September 7, 2010

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2. List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AE(s)	Adverse Event(s)
ALT/SGPT	Alanine aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate aminotransferase
BDI-II	Beck Depression Inventory II
C	Celsius
CAPS	Clinician Administered PTSD Scale
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - IV
EKG	Electrocardiogram
EMDR	Eye Movement Desensitization and Reprocessing
EMEA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
EU	European Union
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
EMEA	European Medicines Agency
LD50	Lethal dose in 50% of cases
LSD	d-lysergic acid diethylamide
MAOI	Monoamine oxidase inhibitor
MAPS	Multidisciplinary Association for Psychedelic Studies
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDMA	3,4-methylenedioxymethamphetamine
MP-1	Sponsor's first Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD

PRN	As needed
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
PTSD	Posttraumatic Stress Disorder
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell Count
RDW	Red Cell Distribution Width
RRPQ	Reactions to Research Participation Questionnaire
SAE(s)	Serious Adverse Event(s)
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for Diagnoses
SERT	Serotonin Transporter
SL	Sublingual
SNRI	Selective Serotonin and Norepinephrine Uptake Inhibitor
SOP(s)	Standard Operating Procedure(s)
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
TSH	Thyroid Stimulating Hormones
U.S.	United States of America
WBC	White Blood Cell Count

3. Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a U.S.-based non-profit research and educational organization supporting research of the therapeutic potential of MDMA (3,4-methylenedioxy-N-methylamphetamine). MAPS is sponsoring clinical trials to test medical uses of MDMA-assisted psychotherapy for patients with chronic disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety related to autism, pain and anxiety related to terminal illnesses and further research into its potential for therapeutic applications. MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA, a pharmacological adjunct that enhances certain aspects of psychotherapy. This Investigator's Brochure (IB) describes the physical, chemical, and pharmacological characteristics of MDMA, its effects in nonclinical and clinical studies, and the safety profile of MDMA-assisted psychotherapy. This IB focuses on research and information relevant to researchers and regulators engaged in clinical trials with MDMA.

MDMA is a ring-substituted phenethylamine that produces anxiolytic and prosocial effects through release of the monoaminergic neurotransmitters with the greatest effect on serotonin, followed by norepinephrine and dopamine. MDMA has been shown to acutely decrease activity in the left amygdala and increase blood flow to the prefrontal cortex in the brain. MDMA has also been found to increase serum levels of the neurohormones oxytocin and arginine vasopressin in humans, which are likely to be involved in increased trust and attenuated reactivity to threatening cues. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, while enhancing communication and capacity for introspection. 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 possibly social anxiety more generally. MDMA may provide a much-needed option in the treatment of PTSD and other conditions associated with anxiety.

A substantial amount of data, both clinical and nonclinical, has been collected over nearly a century of research on the physiological and psychological effects of MDMA in humans and animals. Estimates from animal data suggest a LD50 in humans between 10 - 20 mg/kg [1]. Due a wide range of responses to identical milligram per kilogram (mg/kg) dosing [2], possibly as a result of inconsistent relationship between body weight and pharmacodynamic activity, the sponsor's human trials use fixed doses that are equivalent to between 1 and 2 mg/kg (active doses in studies range from 75mg to 187.5mg) to achieve a more consistent response between subjects. The pharmacokinetics of MDMA in humans have been characterized using oral doses of up to 150 mg MDMA. Onset of MDMA effects occurs 30 to 60 minutes after administration [3, 4], peak effects appear 75 to 120 minutes post-drug [2, 5-7], and duration of effects lasts from three to six hours [5, 6, 8], with most effects returning to baseline or near-baseline levels six hours after drug administration. Unexpected and expected serious adverse events involving administration of MDMA in government-approved clinical trials have been rare and non-life threatening. MDMA produces sympathomimetic effects that include significant transient, self limited increases in heart rate and blood pressure that were likely to be well tolerated by healthy

individuals [2, 4-6, 9-12]. Most people do not experience elevations that exceed those seen after moderate exercise. In the first MAPS Phase 1 safety study, MDMA was found to cause a significant increase in body temperature and heart rate in some healthy volunteers [13]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Risks posed by elevated blood pressure are addressed in clinical trials by excluding people with pre-existing uncontrolled hypertension and by frequently monitoring blood pressure and pulse. Common reactions reported in clinical trials are transient and diminish as drug effects wane during the session and over the next 24 hours. The effects include lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, impaired gait or balance, dry mouth, ruminations, muscle tension and thirst. Less common reactions include restlessness, parasthesias, impaired judgment, perspiration, drowsiness, and nystagmus. While anxiety, headache, fatigue, insomnia and lack of appetite were reported by 40% to 80% of subjects in both placebo and MDMA conditions in MAPS study MP-1 (N=23), tight jaw, nausea, impaired gait/balance, and sensitivity to cold were more often reported by subjects in the MDMA than the placebo condition. MDMA may produce modest changes in immune functioning, lasting up to 48 hours. Because of 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. MDMA was administered to thousands of people prior to scheduling and millions continue to use ecstasy around the world in various non-medical settings [14-18]. While a number of serious adverse events, including fatalities, have been reported after non-medical ecstasy and poly-drug use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use [19, 20]. The common effects in ecstasy and poly-drug use include hyperthermia, psychiatric problems, hepatotoxicity, and hyponatremia. Currently MDMA has been administered to over 850 individuals for research purposes without the occurrence of unexpected drug-related Serious Adverse Events.

To date in the MAPS clinical research program there have been 79 people exposed to MDMA and a total of 210 exposures. MAPS has published results showing clinically and statistically significant improvements in PTSD severity from 20 subjects treated in their first pilot study (MP-1 and MP-1 extension) in the United States (U.S.) [21]. Findings from the long-term follow-up of MP-1 subjects suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [22]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) in 12 subjects suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [23]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. In addition, the sponsor supported an initial pilot study with two experimental sessions comparing full dose to 25 mg active placebo MDMA in Israel that treated five subjects, with no drug-related Serious Adverse Events (SAEs). A dose-response study of MDMA-assisted psychotherapy for PTSD enrolled six subjects, with four receiving MDMA [24] without producing any safety concerns and observing some symptom reduction.

MAPS current program consists of one Phase 1 study of MDMA-assisted psychotherapy in the U.S. and four Phase 2 MDMA/PTSD studies in the U.S., Canada and Israel that are actively recruiting. Ongoing and planned Phase 2 studies of MDMA-assisted psychotherapy for PTSD treatment are laying the groundwork for an End-of-Phase 2 meeting with FDA and Phase 3 multi-site MDMA/PTSD research studies. Based on the experience in chronic, treatment-refractory PTSD, MAPS is exploring new indications for this treatment. Due to similarities in

symptom profiles and to reports from anecdotal research, MAPS is conducting a protocol investigating changes in social anxiety experienced by autistic adults when using two sessions of MDMA-assisted therapy, interspersed with biweekly non-drug integration sessions.

4. Introduction

MDMA:3,4-methylenedioxy-N-methylamphetamine, 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 [25], but is currently not covered by a patent. MAPS currently holds the Drug Master File and an IND for MDMA with the U.S. Food and Drug Administration (FDA). After MDMA was rediscovered by the chemist Alexander Shulgin [26], he and his colleagues provided initial reports of its pharmacology and effects in humans [27, 28]. MDMA was found to robustly influence human emotional status in a unique way [28] without adversely effecting physiological functions or perception, such as visual perception or cognition [3, 5, 7:Vollenweider, 1998 #880].

In the Merck Manual, MDMA is in the entactogen class. Entactogens contain a ring-substituted amphetamine core, and belong to the phenethylamine class of psychoactive drugs. Entactogens as a class of drugs are described as promoting acceptance and compassion for self and others, changing recognition and response to emotions and increased interpersonal closeness. 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. A limited number of exposures to MDMA, spaced approximately a month apart at moderate doses, are sufficient to obtain comparable or better results than other medications that require daily dosing. This infrequent dosing mitigates adverse event frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing.

Shulgin and Nichols were the first to report the effects of MDMA in humans [28]. MDMA-assisted psychotherapy first occurred during the mid to late 1970s after Shulgin introduced MDMA to a psychotherapist. Reported effects of MDMA include enhanced feelings of closeness to others, wellbeing, and insightfulness [29-31]. Prior to scheduling in 1985, MDMA was used in individual, couple, and group therapy to treat diverse psychological disorders, including moderate depression and anxiety [30, 32] [33, 34]. It was also found to be useful in reducing physical pain secondary to certain kinds of cancer [33]. No formal controlled clinical trials of safety and efficacy were conducted at the time [30, 35].

During the early 1980s, increasing numbers of people began using MDMA, sold as "Ecstasy" outside of therapeutic contexts [14]. 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 [17, 36].

MDMA was added to the list of Schedule I controlled substances in the U.S. in 1985, indicating that it has a high potential for abuse and no accepted medical use [37, 38]. Shortly after it was scheduled, animal studies described long term decreases in markers of serotonergic functioning after high or repeated doses of MDMA administration [39] that were not relevant to doses in clinical trials. A recently published meta-analysis took careful steps to overcome methodological limitations in previous work, and found only modest evidence of neurotoxicity [40]. Reports of

adverse events seen following ecstasy use [41-43] and cognitive, physiological, and imaging findings in humans raised concerns regarding the safety of MDMA administration [44-48]. Preclinical studies have often employed inappropriately high doses of MDMA and their findings are open to several interpretations [49, 50], and the vast majority of studies of ecstasy users are retrospective reports in polydrug-using ecstasy users [40, 51]. Classification to schedule 1 combined with the early research in animals and recreational users hampered clinical research into the medical uses of MDMA until the 1990's.

While the initial studies in the 1990s examined the physiological effects of MDMA narrowly from a safety perspective, recent studies have examined the effects of this compound on attention, prosocial effects, memory and brain activity, and human drug discrimination. Findings from an initial report indicated that MDMA-assisted psychotherapy could be conducted safely in people with chronic treatment resistant PTSD[52]. 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, and extroversion, transient increases in anxiety and minor alterations in perception [3, 5-7, 53-57]. In MAPS first Phase 2 study, MP-1, no difference was seen in cognitive function between placebo and MDMA groups after MDMA was given on 2 occasions a month apart in the therapeutic dose range. In addition, published results from the first two Phase 2 studies (MP-1, MP-2) showed significant durable improvements in PTSD symptoms. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA, it appears favorable to pursue the research of MDMA as a medicine used as an adjunct to psychotherapy.

5. Physical, Chemical, and Pharmaceutical Properties and Formulation

MDMA is structurally similar to 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 methylhydrastinine as a phenylisopropylamine derivative of safrole, an aromatic oil found in sassafras, nutmeg, and other plants [1].

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [1, 58]. All 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 [59, 60] and studies of self-administered and experimenter-administered MDMA enantiomers in primates [59, 61-64]suggest that MDMA enantiomers may produce different physiological and rewarding effects, but that 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 methylenedioxyethylamphetamine (MDE) suggest that these different effects of MDMA enantiomers may occur in humans [65]. According to an *in vivo* microdialysis study, S(+)-MDMA may be associated with greater dopamine release in specific brain areas [66]. A recent study in monkeys found that S(+)-MDMA, but not R(-)-MDMA, significantly increased extracellular dopamine levels in the dorsal striatum, whereas S(+)-MDMA significantly increased serotonin levels [63]. MDMA available for human in clinical trials is racemic, containing roughly equal amounts of both enantiomers. Any differential effects of the

enantiomers remain untested in humans.

For clinical trials, the Sponsor used recemic MDMA from two sources. Studies in the United States use MDMA manufactured in 1985 by David Nichols, Ph.D., at the Department of Medicinal Chemistry and Pharmacology, Purdue University, West Lafayette, IN. The MDMA supply for the Sponsor was manufactured as a single lot for use in federally approved clinical research and has been utilized by a number of investigators in the U.S. A stability analysis conducted in 2006 indicates that the compound remains highly stable and pure after 21 years of storage [67]. Studies conducted outside of the U.S. use MDMA from a single batch manufactured in 1998 by Lipomed AG in Arlesheim, Switzerland and maintained by Prof. Rudolf Brenneisen at the University of Bern (Batch number 94.1B5.51). 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. For Sponsor-supported studies, MDMA in the form of white crystalline powder is compounded with inert material into capsules. The capsules are stored in sealable containers placed within a dark safe at ambient temperature. Capsules are administered orally with a glass of water. Details of manufacturing are available from the manufacturers upon request.

MDMA doses in sponsor-supported studies are fixed, rather than based on body weight due to evidence of non-linear metabolism. Full dose is 125 mg, which is equivalent to 1.25 mg/kg (100kg) to 2.6 mg/kg (48kg) for the initial dose. The optional supplemental dose of 62.5 mg is equivalent to 1.3 mg/kg (100kg) to 2.6 mg/kg (48kg). Various comparator doses of less then 125mg of MDMA are also used in the clinical trials.

6. Nonclinical Studies

6.1. Nonclinical Pharmacology

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor. MDMA prevents the uptake of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) and is involved in the release of these three neurotransmitters, with the greatest effects on serotonin release. Receptor binding studies of MDMA employing to very large amounts of MDMA relative to human plasma Cmax found some affinity for specific serotonin, norepinephrine, acetylcholine, and histamine receptors, reporting that strength of activity on these receptors is low in comparison to monoamine transporters [68-71]. *In vitro* studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptake [72, 73] and that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine [74]. MDMA appears to alter the conformation of the serotonin transporter, enabling serotonin to diffuse out of the neuron rather than actively transporting extracellular serotonin into these neurons [75-77]. A recent microdialysis study of a therapeutically relevant dose of MDMA in rats confirms elevated brain serotonin [78]. In combination with other drugs, or at high doses, MDMA may provoke serotonin syndrome, a suite of specific signs and symptoms that can require intervention [79-81]. Participants in sponsor-supported studies are tapered off psychiatric medications that would increase this risk.

6.2. Pharmacology and Product Metabolism in Animals

6.2.1. Pharmacology in Animals

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 intended to develop chemical incapacitants or means of enhancing interrogation [82]. Investigations of the pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA in an attempt to produce human-equivalent doses [83]. Recent reports re-examining these effects have questioned the applicability of interspecies scaling models for MDMA, and have supported nonlinear pharmacology [49, 84, 85]. A study directly comparing MDMA pharmacokinetics in humans and monkeys found that the two species metabolized MDMA in a similar but not identical manner and that MDMA had a shorter half-life in monkeys than in humans. Both species exhibited nonlinear pharmacokinetics, and it appears that monkeys and humans exhibit similar plasma MDMA levels after receiving the same dose of MDMA [86, 87]. An investigation in rats also demonstrated nonlinear pharmacokinetics in that species as well, finding that human-equivalent doses of MDMA in rats are close to or identical to those in humans and drug half-life is rapid [49]. Doses of 10 mg/kg but not 2 mg/kg produced signs of serotonin syndrome in rats, but neither dose reduced total serotonin levels in the brain two weeks after drug administration. These discoveries suggest that toxicological and behavioral studies of MDMA used doses exceeding human equivalent doses. As a consequence, it is difficult to interpret the relevance of findings in nonclinical studies employing these dosing regimes.

Most effects of MDMA on brain receptors likely arise indirectly from monoamine release. For instance, MDMA may cause acetylcholine release and changes in the GABAergic systems through serotonin release and activating $5HT_4$ receptors [88, 89]. MDMA probably stimulates $5HT_{1A}$ receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial $5HT_{1A}$ antagonist in some brain areas [90]. Findings from other studies suggest that it shares qualities with $5HT_{1A}$ agonists. Early studies in rodents suggest that $5HT_{1A}$ receptors reduce anxiety and aggression [91, 92], and some drug discrimination studies suggest that the $5HT_{1A}$ agonist 8-OH-DPAT partially or fully substitutes for MDMA [93-95]. 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 [96, 97]. At least some direct or indirect effects of MDMA on serotonin receptors may cause changes in GABA uptake in the ventral tegmental area of rats [98].

6.2.2. Gene Transcription in Animals

A number of research teams have studied the effects of MDMA on gene expression in rodents [99-102]. However, many of these reports used 10 to 20 mg/kg MDMA, and it is unlikely that these changes can be generalized to humans given lower doses. These studies report an increase in expression of genes that regulate the GABA transporter [99, 102]. Some of the increases in transcription are in genes associated with monoamine release [99]. Investigations with serotonin transporter knockout mice suggest that at least some of these changes in gene transcription are related to serotonin release [99]. Examining rat brains two weeks after repeated MDMA detected a sharp drop in serotonin gene transporter expression [103], offering an alternative to axonal

damage as an explanation for alteration in serotonergic function after repeated doses of MDMA. A recent publication found that repeated administration of MDMA at 1 or 5 mg/kg weekly for four weeks increased transcripts for $5HT_{1B}$ receptors in various brain regions and $5HT_{2C}$ receptors in the cortex and hypothalamus [104]. Increases in transcripts of genes regulating extracellular signaling in mice were also reported [105]. It appears that serotonin may play more of a significant role than dopamine in transcription-level changes [104]. Transcripts were assessed ten hours after the last of repeated MDMA administrations and it is not clear 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 changes in proteins produced from the genes. Future studies will need to separate direct and indirect effects of MDMA on gene expression.

6.2.3. Endocrine Effects in Animals

In rats, large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin [106-108], with elevation lasting up to four hours after dosing, and with hormone levels attenuated by a $5HT_2$ receptor antagonist. Given the large dosage used, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. A study of isolated rat hypothalamus reported arginine vasopressin (AVP) and oxytocin release after administration of MDMA and its metabolite HMMA [109]. A recent study using 1-3 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 [63]. Fluoxetine attenuated prolactin release after administration of racemic MDMA, and fluoxetine and a 5HT2A antagonist attenuated prolactin release after R-(-)-MDMA, indicating that prolactin release is associated with serotonin release and action on 5HT2A receptors by R(-)-MDMA.[64].

6.2.4. Thermoregulatory Effects in Animals

Rodents have generally been used to study the hyperthermic effects of MDMA. Given that rodents have a much smaller body mass and do not perspire, it is unlikely that thermoregulation occurs in the same way in rodents and humans [110]. Moderate and high doses of MDMA elevate body temperature and disrupt thermoregulation in rodents [76], and doses of MDMA in the 1 to 2 mg/kg range only cause a slight increase in body temperature [111]. MDMA causes susceptibility to changes in ambient temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperatures producing hypothermia [112-114]. High doses of MDMA also produce significant elevations in body temperature in primates [84, 115, 116]. At doses closer to those humans ingest [117], monkeys exhibit only slight to moderate elevation in body temperature [118, 119]. In contrast to findings in rodents, primates are not susceptible to changes in ambient temperature when they receive MDMA, exhibiting slight to moderate increases in body temperature regardless of the temperature of the environment [117-119], 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 in after MDMA and cool temperatures and higher body temperatures in another group given MDMA in a warm temperature [120]. It appears that findings in rodents do not extrapolate well to primates,

and studies in humans supported by the Sponsor will address the effects of moderate doses of MDMA on thermoregulation.

6.2.5. Cardiovascular Effects in Animals

In vivo assessments of cardiovascular effects of MDMA in animals detected increased sympathetic activity, as seen in humans [76]. Injections of 20 mg/kg MDMA in conscious rodents assessed by radiotelemetry found that MDMA caused a prolonged increase in blood pressure [121]. In the same study, MDMA was found to produce mild isotonic contractions of rat aorta and vas deferens vascular tissue in anesthetized rodents, but could also inhibit prejunctional contractions evoked by stimulation [121]. An injection of 2 mg/kg MDMA elevated heart rate in rabbits [122]. The researchers found that MDMA has both pressor and depressor effects, acting through adrenergic receptors [121, 123, 124]. A study in rodents suggests that norepinephrine may play a role in cardiovascular effects [125]. Given the affinity of MDMA for the norepinephrine transporter, it is possible that the cardiovascular effects of MDMA could be attributed to norepinephrine signaling in the peripheral nervous system.

6.2.6. Behavioral Effects in Animals

In rodents, doses of MDMA equivalent to human doses produce either few or no behavioral effects. However, doses of 5 mg/kg or greater have several specific behavioral effects, including increased locomotor activity, increased anxiety at moderately high doses, and decreased anxiety at higher doses [76, 126]. Rats given lower doses of MDMA exhibited increased anxiety in the elevated plus maze [127], while rats given higher doses exhibited reduced anxiety on the maze. Rats given higher doses also reduced aggressive behavior as well as social investigation. Rodents responded to very high doses of MDMA by exhibiting flat body posture, forepaw treading and an erect tail ("Straub tail"), all signs of rodent serotonin syndrome [126]. MDMA produces some repetitive behavior in rodents, but not to the same degree as psychostimulants. MDMA leads rats to walk around a cage perimeter, interpreted as an indicator of thigmotaxis, which is a sign of anxiety [76]. However, it is notable that a recent publication failed to find thigmotaxis in rats given 5 mg/kg MDMA [128]. In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA [119].

To date, no empirical investigations have been conducted on the effects of MDMA on primate social interactions. 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 [96]. Recent studies conducted by the same team of researchers suggest that MDMA increases prosocial behavior in rats by elevating oxytocin in the paraventricular nucleus through 5HT1A receptor agonism, with the oxytocin increase arising from the indirect effects of MDMA on 5HT1A receptors [97, 129]. To date, there have been no human pharmacological challenge studies combining MDMA with 5HT1A agonists, while 5HT1A antagonists have negligible effects on subjective or physiological effects of MDMA in humans [57, 130-132]. 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 [8, 15, 133, 134].

6.3. Toxicology

6.3.1. Neurotoxicity in Animals

Repeated high doses of MDMA in animals reduce total serotonin levels in the brain, impair transport of serotonin, and cause psychobehavioral changes such as increased anxiety [76, 126, 135-137]. Studies in rodents and primates suggest that MDMA could damage serotonin axons and cause neurotoxicity [76, 138-141]. However, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses, an issue that remains true even in recent investigations [see for example50, 142, 143]. It now appears that lower doses of MDMA do not reduce brain serotonin [84, 85]. 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 [144]. Rats receiving lower doses of MDMA also fail to exhibit signs of neurotoxicity [85]. A recent report detected increases in one marker of neuronal injury without detecting any decreases in brain serotonin after administering two human-equivalent doses of MDMA to rhesus monkeys for two days [145]. Relying on previous *in vitro* and *in vivo* research and on their own current work, the same researchers present a case that MDMA is altering regulation of brain serotonin without producing damage to serotonin axons. They reach this conclusion through comparing findings of reduced brain serotonin and SERT with failure to detect other indicators of neuronal injury and findings of decreased expression of the SERT gene in rat brain [50].

6.3.2. LD50 in Animals

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 [82]. The LD50 in mice housed together is 20 mg/kg, considerably lower than values in isolated animals [113, 146]. MDMA lethality also varies between the sexes and different strains in rats.[147-149].

6.3.3. Developmental Toxicity in Animals

15 mg/kg MDMA administered s.c. to pregnant rats was detected in amniotic fluid [150]. Several teams of researchers have performed studies of developmental toxicity in rodents. None of the studies found gross structural abnormalities in rats exposed to high doses of MDMA *in utero.* In an initial study, pregnant rats were administered twice-daily injections of high doses of MDMA (15 mg/kg) or saline from embryonic days (E) 14-20. Rat pups that had received MDMA showed reductions in the dopamine metabolite homovanillic acid, along with reductions in the serotonin (5-HT) metabolite 5-HIAA. Prenatally exposed MDMA animals also had reduced dopamine and serotonin turnover in the nucleus accumbens [151]. 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. Brain-derived neurotrophic factor (BDNF), which controls neuronal growth in the brain, was significantly increased (19-38%) in all forebrain structures and in the brainstem in MDMA-exposed neonates [152]. The researchers proposed that BDNF was compensating to minimize MDMA effects. However, later studies found that neonatal MDMA exposure did not affect hippocampal concentrations of serotonin or dopamine [153] and that a region-specific enhancement in BDNF expression did not mediate the abnormal

serotonergic signaling observed following neonatal MDMA exposure [154]. Postnatal days 11 and 20 were proposed to be equivalent to the third trimester of gestation in humans [152], 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.

Prenatal MDMA exposure at high doses significantly increased locomotor activity of pups in a 20-min novel cage environment [151]. Rodents treated with MDMA during development were not significantly different than rodents who received MDMA as adults. The results of several behavioral tests did indicate that developmental MDMA exposure combined with adult exposure may interfere with some aspects of learning [153]. Neonatal MDMA administration did not alter working memory in the object-recognition test in young adulthood (PD 68-73) and there were no differences in binding of the radiolabeled SSRI citalopram to the serotonin transporter 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 [155]. Another team also found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA [156]. A study in neonatal rats suggests two distinct critical periods wherein repeated doses affected learning versus acoustic startle [157].Given differences between human and rodent development and thermoregulation, it is not clear whether such findings can be generalized to humans (see Section 6.2.4). Because 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.

6.3.4. Self-Administration in Animals

Mice, rats, and monkeys will self-administer MDMA, indicating that MDMA has rewarding properties in animals [158-160]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [158], but they reduced their MDMA intake over time. While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine [161, 162]. Taken together, these results suggest that the abuse liability of MDMA is moderate.

7. Effects in Humans

Evidence exists for intentional human use of MDMA as early as the late 1960s [26], and there are records of a police seizure of MDMA in the early 1970s [163]. Shulgin and Nichols were the first to report on the effects of MDMA in humans [28]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety [30]. Legal therapeutic use continued until its placement in US Schedule 1 in 1985 [29, 33, 164]. Estimates indicate that 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling [26, 164]. A few uncontrolled human studies of MDMA occurred in the 1980s [9, 165], including Greer and Tolbert's study of MDMA in a psychotherapeutic context. Recreational use of MDMA, known as "ecstasy," has been ongoing since the early 1970s, but controlled human studies of MDMA did not commence until the early to mid-1990s, with the publication of a Phase 1 dose-response safety study supported by the Sponsor and conducted by Grob and colleagues [13]. The Sponsor has completed two

investigations of MDMA-assisted psychotherapy for PTSD, one in the U.S. and one in Switzerland [21, 166, 167] with additional phase 2 studies underway.

7.1. Pharmacology and Product Metabolism in Humans

7.1.1. Pharmacology in Humans

Estimates from animal data suggest the LD50 in humans is probably between 10 - 20 mg/kg [1]. 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 subjects. The pharmacokinetics of MDMA in humans have been characterized in blood and urine samples using oral doses of up to 150 mg MDMA.

Many researchers categorize MDMA as belonging to a unique class of drugs referred to as the entactogens [8, 31], 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 [3, 6, 7, 168], as well as a small number of pharmacologically related compounds, such as methylenedioxyethylamphetamine (MDE) [168]. Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecstasy [15, 133, 134, 169]. Initial studies measured self-reported empathy or closeness to others in healthy volunteers [2, 5, 55], and recent controlled studies measured effects of MDMA on social cognition or emotion [53, 54, 56]. Although researchers have offered several models and explanations for the effects of entactogens, it appears that serotonin release plays a significant role in producing at least some of these effects, and norepinephrine release may play a lesser role. Indirect action on $5HT_{1A}$ or $5HT_{2A}$ receptors and neuroendocrine responses such as increases in the hormones oxytocin, vasopressin, prolactin, and cortisol may also play a role in producing the unique effects of MDMA.

Preventing serotonin release through administration of selective serotonin reuptake inhibitors (SSRIs) appears to attenuate or eliminate most subjective, physiological and immunological effects of MDMA [170-174]. Pre-treatment or co-administration with SSRIs attenuates the effects of MDMA on mood and perception without influencing specific effects such as nervousness or excitability [170]. Some researchers report that SSRIs attenuate MDMA-induced increases in heart rate and blood pressure [171, 174] while others report that SSRIs only attenuate elevated heart rate [173]. All three studies of SSRI pre-treatment suggest that co-administration of SSRIs with MDMA is safe, but that this combination prevents or significantly reduces the subjective effects of MDMA. These subjective effects are predominately mediated by direct or indirect action on $5HT_{2A}$ receptors [57, 132, 175], with at least one study concluding that the effects of MDMA upon positive mood are at least due in part to 5HT2A receptor activation [57]. In contrast, the $5HT_{1A}$ receptor appears to be minimally involved in producing the subjective effects of MDMA[57, 130-132]. 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 actually attenuating MDMA-related reduction in performance on a task requiring visual attention, and coadministration of pindolol to 9 men and 8 women failed to alter the acute effects of 75 mg MDMA on self-reported mood [57, 130].

Recent human MDMA studies suggest that norepinephrine (NE) release may also contribute to the pharmacodynamic, physiological and psychological effects of MDMA [176-179]. Studies with NE uptake inhibitor reboxetine suggests that norepinephrine plays a role in the cardiovascular effects of MDMA and on subjective effects on positive mood and excitement [177]. Most of the psychostimulant-like and psychological effects of MDMA are blocked after administration of the dual SSSR/NRI duloxetine [178, 179], and there is evidence that norepinephrine and serotonin may play a role in elevated copeptin, a neuroendocrine hormone, in women after MDMA [179]. Preclinical and *in vitro* findings reports indicate that MDMA displays a higher affinity for the norepinephrine transporter than the serotonin transporter [73], which could possibly explain these results (Hysek/2012).

At least some MDMA effects on mood and anxiety may result from dopamine release indirectly activating D_2 receptors, as administering the D_2 antagonist haloperidol diminished positive mood and increased anxiety in humans [180]. As of November, 2012, there have been no studies in healthy volunteers examining the role of dopamine release or uptake inhibition.

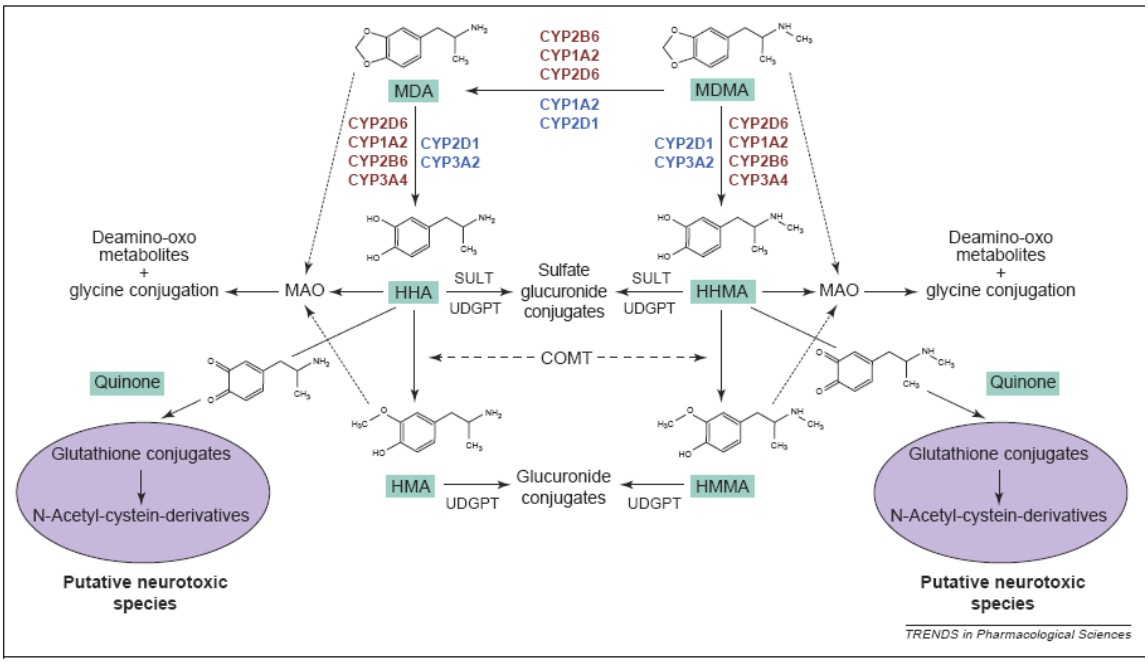

Figure 1. Metabolism of MDMA in humans (in red) compared to metabolism in rats (in blue). Reproduced with permission of R. de la Torre [181].

7.1.2. Metabolism in Humans

Metabolites of MDMA are summarized in Figure 1 [182-186]. Metabolites are primarily excreted as glucuronide and sulfate conjugates [183]. Studies examining metabolism of 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates [187-191]. Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery [191]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [192]. As was the case for maximal plasma values, urinary

recoveries for MDMA and MDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA [187]. 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 [193], suggesting that secondary metabolism of MDMA continues during this period. 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 [194]. Findings support the enantioselective metabolism of MDMA and its metabolites measured in blood and urine [195, 196].

Onset of MDMA effects occurs 30 to 60 minutes after administration [3, 4], peak effects appear 75 to 120 minutes post-drug [2, 5-7], and duration of effects lasts from three to six hours [5, 6, 8], with most effects returning to baseline or near-baseline levels six hours after drug administration. Self-reported duration of effects may increase with as the dose of MDMA increases [2]. Orally administered MDMA has a half-life of seven to nine hours in humans, with one report listing a half-life of 11 hours [188]). It 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. Because O'Mathuna and colleagues present evidence that CYP2D6 activity may not fully recover until ten days after MDMA [197, 198]. 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 [199]. In contrast, MDMA may produce increased activity of the enzyme CYP1A2, as evidenced by comparing caffeine metabolism before and after MDMA [200]. The enzyme COMT and monoamine oxidase may also be involved in the metabolism of MDMA [192]. At least one variation in COMT genotype may affect MDMA elimination rate (Ke) and systolic blood pressure (SBP) after MDMA [201].

7.2. Physiological Effects in Humans

7.2.1. Endocrine Effects in Humans

MDMA acutely increases cortisol, prolactin, and adrenocorticotropic hormone concentrations in a dose dependent manner [4, 5, 13, 56, 187, 202], whereas growth hormone is unchanged by up to 125 mg MDMA [4]. Increases in cortisol and prolactin peak at about 2 hours after MDMA administration [4, 13]. A second dose of 100 mg MDMA, given four hours after an initial 100 mg, produces a second increase in cortisol during an interval when cortisol levels are declining [203], and a dose of 100 mg MDMA, given 24 hours after an initial dose, stimulates a greater release of cortisol but not prolactin [187]. A naturalistic study in clubgoers found a much greater elevation in cortisol after ecstasy use [204]. 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 [5]. MDMA produces a robust increase in the neurohormone oxytocin [54], a finding first seen in a naturalistic study [205]. The naturalistic study reported elevated levels of the hormone oxytocin in clubgoers with detectable blood MDMA levels when compared to clubgoers without any detectable levels of MDMA. It is likely that all neuroendocrine changes result from monoamine release, and it is currently

unknown what role, if any, they play in producing the effects of MDMA. 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 [206-209].

The significance of elevated oxytocin in producing changes in social cognition are discussed in section 7.1, and include potentially therapeutic effects, such as increased feelings of closeness to others or greater ability to detect expressions of positive mood in others. The significance of elevated cortisol after MDMA is unclear. It is possible that cortisol elevation could be tied to specific acute effects on mood or memory. However, 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 and without altering the effects of MDMA on mood, [210]. It is unclear what contributions, if any, elevated cortisol make to the subjective or physiological effects of MDMA.

7.2.1.1. Endocrine Effects and Homeostasis in ecstasy users

A number of case reports describe hyponatremia after uncontrolled, non-medical ecstasy use [83, 211-213]. Behavioral factors, including vigorous exercise and excessive consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones arginine vasopressin and oxytocin, likely all contribute to this very rare but serious adverse event in ecstasy users [205]. Hyponatremia has not occurred during a controlled clinical trial with MDMA.

7.2.2. Thermoregulatory Effects in Humans

In the first Phase 1 safety study funded by the Sponsor, MDMA was found to cause a significant increase in body temperature and heart rate in some healthy volunteers [13]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Doses between 1.5 and 2 mg/kg MDMA produced only a slight elevation in body temperature that was not clinically significant [6, 171, 175] and this elevation was unaffected by ambient temperature [117]. 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 [117]. The same study found that ambient temperatures did not affect elevation in core temperature after administration of MDMA, which increased metabolic rate. A second dose of MDMA elevates body temperature, but not beyond what would be expected after the cumulative dose [194].While MDMA did not increase or decrease perspiration overall, it was associated with a higher core temperature when people began perspiring. Ambient temperature neither attenuated nor amplified the subjective effects of MDMA, with people reporting similar drug effects in the warm and the cool environment. 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 participants given MDMA found that men exhibited a greater elevation in body temperature than women when given the dose of MDMA in milligrams per kilogram [6]. Subsequent studies have not confirmed this gender difference [11], and a report in a sample of 17

men and women reported higher oral temperatures in women [201]. 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 most drug effects. It may be the case that ambient temperature and vigorous exercise contribute to the occurrence of hyperthermia in people ingesting ecstasy in uncontrolled settings. However, one out of two naturalistic studies reported that ecstasy users had a slight but not statistically significant increase in body temperature, while two others failed to find any significant differences in ecstasy-user body temperature at a club [204, 214, 215].

Hyperthermia has occurred in people using ecstasy in unsupervised and non-medical conditions, and though rare, it is one of the most frequently reported serious adverse events occurring in ecstasy users [212, 216]. The exact conditions preceding hyperthermia are unknown. Even if ambient temperature does less to moderate the effects of MDMA on body temperature than originally believed, other environmental and behavioral factors, as those related to vigorous exercise, may be involved. 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 [217]. A case report and some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans [218, 219]. No cases of hyperthermia have been reported in clinical trials with MDMA.

7.2.3. Cardiovascular Effects in Humans

MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing [9] and replicated by other research teams in the US and Europe [4, 6, 10]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [2, 5, 11, 12]. Most people do not experience elevations that are greater than those seen after moderate exercise. Cardiovascular effects of MDMA first appear 30 to 45 minutes after administration [9] and peak between 1 and 2 hours post-drug [7, 10], 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 greater elevation in heart rate in a study summarizing and pooling data from a series of human MDMA studies [6]. These studies did not report any discomfort or increased distress accompanying cardiovascular effects.

Elevation in blood pressure above 140/110 or higher occurred in approximately 5% of research participants receiving a single dose of at least 100 mg MDMA in research studies [4, 8]. Peiro and colleagues observed elevation in blood pressure above 150/90 as well in all ten participants given 50 mg followed two hours later by 100 mg MDMA [194]. None of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [4, 8, 194].

The alpha(1) – and beta-adrenergic receptor antagonist carvedilol reduced MDMA-induced elevations in blood pressure, heart rate, and body temperature when administered 1 h before MDMA without affecting the subjective effects of MDMA. Hence carvedilol could be useful in the treatment of cardiovascular and hyperthermic complications associated with ecstasy use [220].Other antihypertensive medications either alter some of the effects of MDMA [221] or do not significantly reduce blood pressure [176].

As described above, administering 50 mg MDMA followed two hours later by 100 mg produces elevated HR and BP, but the elevations are no greater than those expected with plasma MDMA levels [194]. The study used a different dosing regimen than the one used in sponsor-supported studies.

The elevation of blood pressure and increased heart rate produced by MDMA, like that produced by other sympathomimetic drugs, can lead to additional risks and complications [222-224], such as stroke, cardiac events, or other cerebrovascular events, including cerebral venous sinus thrombosis [225] and cerebral or subarachnoid hemorrhage [41, 226-229]. In two such cases, a previously existing underlying arteriovenous malformation appeared to play a role in the event [226, 228]. Increased heart rate (tachycardia) and elevated blood pressure can also lead to cardiac events, such as arrhythmias or myocardial infarction [230, 231]. 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 expressed concern that MDMA activity at $5HT_{2B}$ receptors might be indicative of increasing risk of valvular heart disease with repeated use [69]. Studies in ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential valvular heart disease [232], and a case of valvular heart disease has occurred in a man reporting approximately 16 years of ecstasy use [233]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Previous to this, ECGs in eight ecstasy users also failed to find any cardiac abnormalities [10]. 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.

7.2.4. Liver Effects in Humans

Hepatotoxicity (liver disease or damage) was reported in approximately 16% of 199 case reports from non-medical, uncontrolled ecstasy users collected from the mid-1990s to 2001, making it the third most common serious adverse event in reported in the literature [83]. There appears to be more than one pattern of ecstasy-related hepatotoxicity, and a number of factors, including polydrug use and setting of use may be involved [234]. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet [235-237]. In other cases, hepatotoxicity has occurred after months of regular ecstasy use [238]. Standard toxicity studies failed to find liver damage after MDMA in rats or dogs after 28 days of exposure [239], nor have any cases of liver disease arisen during controlled studies. Examinations of case reports and a number of *in vitro* studies suggests an association between hyperthermia and hepatotoxicity. However, liver disease also occurred in some individuals without the occurrence of hyperthermia, with it appearing after continued use and resolving after abstinence. In these cases, it appeared after continued use and resolved after a period of abstinence. These reports suggest a potential immunological response. Because hepatotoxicity has been noted in ecstasy users, *in vitro* and *in vivo* studies have examined the hepatotoxicity of MDMA. These studies show that high doses of MDMA can impair liver cell viability [240], increase profibrogenic activity in cultured stellate cells [241], and slightly reduce cell viability without producing lipid peroxidation [242]. However, peak liver exposure to MDMA in Sponsor studies should be

approximately one-eleventh the concentration shown to impair cell viability in these *in vitro* studies. No cases of liver disease or hepatotoxicity have occurred in a controlled clinical trial with MDMA.

7.2.5. Immunological Effects in Humans

Studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects [172, 203, 243, 244]. 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-2 and interferon-Gamma, and increased production of anti-inflammatory cytokines, including IL-4 and IL-10. Generally, MDMA appeared to decrease the concentration of Th1 (immunostimulating and pro-inflammatory) cytokines and increase the amount of Th2 (immunosuppressive and anti-inflammatory) cytokines measured in blood. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [244, 245]. Because of 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. Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given four hours after the first dose [203, 246]. 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 [203]. 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 first dose. Previous Phase 1 studies have not reported any indication of increased risk of illness occurring after MDMA administration.

7.2.5.1. Immunological Effects in Ecstasy Users

A longitudinal study of regular ecstasy and cannabis users found a sustained reduction in interleukin 2 (IL-2), increased levels of transforming growth factor-Beta (TGF-B) 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 [247].

7.2.6. Effects on Sleep in Humans

Serotonin and catecholamine neurotransmitters are known to modulate sleep architecture and alertness. To date, there is only a single study examining the acute effects of MDMA on sleep [248] while all other investigations have looked at sleep in ecstasy users. In a trial with 2 mg/kg MDMA given six hours prior to preparing for sleep, MDMA was found to increase Stage 1 sleep and reduce rapid eye movement (REM) sleep without producing an increase in daytime sleepiness [248].

7.2.6.1. Effects on sleep in ecstasy users

Examining sleep architecture in ecstasy users, the same investigators found less total sleep time and less stage 3 and 4 sleep on the adaptation night, but no overall differences in sleep architecture [248]. Another study comparing heavy ecstasy users with non-drug using controls

found no differences in baseline sleep using electroencephalography (EEG) [249]. Early studies in mostly heavy ecstasy users reported significant decreases in total sleep as well as stage 2 sleep [250], while recent studies 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[251, 252]. Findings of sleep disruption in ecstasy users are not likely 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 [253]. 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 [248, 249], 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.

7.3. Reproductive and Developmental Risks in Humans

Previous research supported a possible link between ecstasy use and birth defects [254], 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 [255]. 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 [256]. 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 [257].

There are no plans to include pregnant women in research studies with MDMA.

7.4. Abuse Potential in Humans

Studies in humans and animals suggest MDMA possesses some abuse potential. Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with ecstasy abuse and 0.6% with dependence [258], though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence [259], and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency [260]. When reviewing the effects of MDMA in a sample of 74 largely drug-naïve participants, 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 [6]. Only one of 32 participants enrolled in sponsor-supported studies of MDMA-assisted psychotherapy for PTSD reported taking ecstasy outside the confines of the study and failed to reproduce the experience [166]. Several participants volunteered that they would not seek out ecstasy outside of therapy. All 12 participants enrolled in the study of MDMA-assisted psychotherapy in Switzerland did not test positive for stimulants or MDMA

[167]. It also appears that MDMA 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. Hence MDMA possesses moderate abuse liability that is greater than that for serotonergic hallucinogens but less than that for stimulants.

7.5. Neuropsychological Effects in Humans

7.5.1. Subjective Effects in Humans

MDMA alters mood, perception, and cognition. At doses of at least 1 mg/kg (or approximately 70 mg) and higher, active doses of MDMA alter mood and cognition and produce slight alterations in perception [6, 261]. Effects peak 90 to 120 minutes after oral administration and they are near to or at pre-drug levels three to six hours later [8, 262, 263]. Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later [5, 264, 265]. Most of the therapeutic effects of MDMA result from changes in affect, cognition, and social interaction. When combined with psychotherapy that supports one or more of these effects, MDMA permits people to confront and consider emotionally intense memories, thoughts, or feelings, and perhaps through changes in mood and perception, increases empathy and compassion for others and the self [24, 165, 266]. Though a naturalistic study reported that ecstasy increased accuracy of assessing at least some emotional expressions [267], a controlled study with 0.75 and 1.5 mg/kg MDMA failed to replicate this finding [11].

7.5.2. Emotional Effects in Humans

MDMA increases positive mood and anxiety [3, 5-7]. MDMA users report feeling more talkative and friendly after receiving MDMA, Self-reported interpersonal closeness was noted during a study in healthy volunteers [8]. Subsequent research confirmed the occurrence of increases in interpersonal closeness after MDMA [53-56, 173]. 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 [5], possibly due to the low sensitivity of this measure. However, a recent investigation into the effects of pretreatment with the SSRI paroxetine on MDMA effects in humans reported that MDMA increased feelings of being social and closeness to others, and that paroxetine reduced these effects [174]. People reported feeling anxious and undergoing negatively experienced derealization, including increased anxiety related to loss of control and experiences of racing or blocked thoughts [3, 6, 8].

People receiving active doses of MDMA experienced euphoria, positive mood, vigor, and positively experienced derealization, consonant with early retrospective reports, and they also experienced anxiety, tension, and dysphoria, as concern over losing control over the self [3, 5-7]. More surprisingly, participants report increased positive mood even after a dose of 25 mg [268]. It is uncertain whether the increases in positive and negative mood occur simultaneously or occur at different times throughout the duration of MDMA effects; there is some suggestion in reports from two different teams that peaks in negative mood may precede peaks for positive mood [7, 180]. MDMA may have a greater impact on mood in women than in men. Women report greater elevation in negative mood. A second dose of MDMA does not increase subjective effects beyond effects reported after an initial dose, results which Peiro and colleagues interpreted as

indications of tolerance to these effects [194]. It is notable that the second dose in this study was double that of the first dose, in contrast to sponsor-supported studies, wherein the second dose is half the size of the initial dose.

Positron emission tomography (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 [269]. Decreased activity in the amygdala may be indicative of reduced reactions to potential threats [270]. An fMRI study conducted by Bedi and colleagues found that 1.5 and 0.75 mg/kg MDMA reduced signaling in the amygdala in response to angry faces when compared with placebo, though without changing the response to faces showing fear [11]. 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. Complimenting these findings are results from Hysek and colleagues demonstrating that MDMA enhanced the accuracy of recognizing faces exhibition expressions of positive mood, impaired mind reading for facial expressions of negative mood, and had no effect on mind reading for neutral stimuli [56]. Hysek suggests that the enhanced mind reading of positive emotions may facilitate therapeutic relationships in MDMA-assisted psychotherapeutic settings. There is also some evidence for MDMA producing selective difficulty in recognizing faces expressing fear Baggott, 2008 #1606}.

7.5.2.1. Emotional effects in ecstasy users

Retrospective surveys of people who have used MDMA or ecstasy offer similar accounts of MDMA effects to those reported in controlled studies. These studies surveyed or interviewed members of several populations, including college students, psychotherapists, and individuals recruited via word of mouth or in public spaces. Study respondents report experiencing stimulant-like effects, such as greater energy or talkativeness, and hallucinogen-like effects, including as perceptual changes or poor concentration. They also report that ecstasy increased feelings of closeness, compassion, or empathy toward the self or others [15, 133, 134, 271]. 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.

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 [83]. 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 as psychotic response, as seen in [272]. 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 that pre-existing psychiatric problems occur in people who choose to use ecstasy [273] 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 [216, 274]. 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.

Previous reports have found an association between ecstasy use and increases in symptoms of depression or anxiety, (see for example [275, 276]). 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 [277]. 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 [278-281]. One found an equal or stronger association between regular use of cannabis, and not ecstasy, and anxiety, depression or other psychological problems [282].

7.5.3. Effects on Perception in Humans

Study participants receiving MDMA experienced slight changes in visual or auditory perception, including changes in the brightness of the room or colors, sounds seeming closer or farther away, and simple visual distortions [2, 3, 5, 6]. Participants also experienced altered time perception and changed meaning or significance of perceptions after MDMA [8]. People maintained insight as to their experience, and there was little indication that MDMA produced any strong alterations to the sense of self or control over the experience [5, 7]. Healthy volunteers reporting unusual beliefs retained a degree of insight [5]. Women reported experiencing all subjective effects of MDMA more intensely, but especially those related to perceptual changes [6]. The perceptual effects of MDMA appear to be the result of direct or indirect action on $5HT_{2A}$ receptors, as coadministration of the $5HT_{2A}$ antagonist ketanserin reduced reported perceptual alterations as well as eliminating slight elevations in body temperature after 1.5 mg/kg MDMA [175], while co-administration with the 5HT1A antagonist pindolol did not [130].

7.5.4. Cognitive Effects in Humans

MDMA does not affect responses on tasks requiring attention and response to visual stimuli or visually presented words [8, 269], but interferes with performance on digit-symbol substitution, a measure of attention, psychomotor speed and visual memory [3]. 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 in driving cars [262]. A recent series of studies conducted in the Netherlands that 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 [283-286]. 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 [287]. MDMA acutely improved performance on one measure of impulsivity while failing to affect performance on other impulsivity measures [284]. 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 [283, 286, 287]. Administering a 5HT2A receptor antagonist but not a 5HT1A 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 [132]. These changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

In the sponsor-supported study of MDMA-assisted psychotherapy in people with PTSD, Mithoefer and colleagues did not detect significant differences in cognitive function between participants who received two doses of MDMA and participants who received placebo [21]. These findings suggest that MDMA given within a clinical trial does not produce impaired cognition.

7.5.4.1. Long-term cognitive effects in ecstasy users

Many investigations have examined cognitive function in ecstasy users. 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 may be a significant effect of ecstasy use on verbal memory, and a lesser effect on visual memory [40]. Two meta-analyses of memory in ecstasy users arrived at somewhat contradictory conclusions [288, 289]. 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[288], 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 [289]. 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 [290], but found no significant relationship between lifetime ecstasy use visuospatial task performance.

The only study attempting to address effects of ecstasy use on cognitive function in middle aged versus younger users and 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 [291].

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 [292]. 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 subjects in Schilt's study with controls, and failed to find any significant differences in working memory and selective attention [293].

The nature and strength of the association between regular ecstasy use and impaired executive function remains inconclusive, with some reports finding impaired executive function in ecstasy users [18, 294, 295], and others finding no association [296], or finding executive function impairments only in male ecstasy users [297]. 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) [298]. Polydrug use likely contributes to findings of impaired executive function seen in ecstasy users [280, 299]. Current research has not settled the question.

Investigations of the interaction between genotype and regular ecstasy use have supported differential effects upon reward-based attention or visual or verbal memory [300-302]. Given the small samples and uneven numbers with different genotypes, any conclusions await further support.

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, as seen in [45, 303]. Recent studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions [304-306]. Two recent studies using the same measure of behavioral impulsivity in samples of heavy ecstasy users yet obtained different findings [304, 306]. 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 studies published in the last two years suggest that polydrug use may be equally or more strongly related to impulsivity in ecstasy users [265, 307, 308]. The relationship between drug use, including ecstasy use, and impulsivity, is complex.

Not all studies report that ecstasy users fare worse on measures of cognitive function than controls. A number of recent reports detected little or no significant differences between ecstasy users and polydrug user controls in performance on tasks of cognitive function [293, 306, 309-313]though other studies continue to find consistent differences, particularly in verbal memory [252, 314-317]. Regular use of many substances, including alcohol, may affect cognitive function, with ecstasy being only one of those substances [318]. Several reports have found relationships between cognitive function and use of other drugs as well as or instead of ecstasy[301, 309, 311, 314, 319, 320].

7.5.5. Brain Activity In Humans

Brain imaging recorded during a task requiring keeping a target cue in mind, attention, and response inhibition also found changes in parietal activity when comparing performance under placebo or 75 mg MDMA [321]. MDMA increased activity in frontal areas and decreased activity in occipital sites as measured via fMRI [322], Subjects 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 user participants receiving a minimum dose 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 [323]. However, a comparison between

heavy ecstasy users and non-user controls failed to find differences in baseline rCBF [269], and a report assessing changes before and after initial use found increased rCBF in only one area of the prefrontal cortex [324], suggesting that the changes seen by Chang and colleagues are a transient effect. Electroencephalography (EEG) recorded two hours after MDMA administration showed the following changes in EEG activity: overall increase in beta activity, reduction in alpha activity, and specific decreases in alpha and delta in frontal areas and increased frontotemporal beta signal [325]. The authors reported these EEG patterns as being similar to those seen with serotonergic and noradrenergic drugs, as well as, to a lesser extent, with dopaminergic drugs.

7.5.5.1. Changes in brain activity in ecstasy users

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 [326]. 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 [327]. A prospective study comparing brain activity before and after use of ecstasy failed to detect differences in working memory, attention or brain activity [293], suggesting a relationship between repeated, regular use of ecstasy and other drugs and changes in brain activation.

Researchers using slightly different methods have reported differing results. These include finding no differences between ecstasy user and polydrug user control in SERT sites [328], modest reductions in estimated SERT sites in ecstasy users versus non-drug using or cannabis-using controls [329], and an association between decreased SERT sites and lifetime ecstasy use [330]. This study also reported finding slightly fewer 5HT2A sites in both "ecstasy preferring" and "hallucinogen preferring" groups. Studies in very moderate ecstasy did not report an increase in this marker [324], and only one of three studies heavy users detected a change in 5HT2A receptor density. [331-333]. 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 [324, 334]. 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 [335].

7.6. Long Term Effects in Ecstasy Users

Spurred on by nonhuman animal studies that found that 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 [44-46, 336], and as described in the sections above. Early investigations possessed a number of methodological flaws, including retrospective design and poor matching of ecstasy users with appropriate controls [51, 83, 337]. 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 psychoactives, including alcohol [294, 296, 338, 339]. Some of these investigators also conducted longitudinal studies, comparing ecstasy users, sometimes alongside controls, at two separate time points [340-342]. Most studies suggested that heavy but not moderate ecstasy users had impaired verbal memory

and lower numbers of estimated SERT sites, with heavy use often defined as being at or greater than 50 times or tablets. Taken together, there is some risk of long-term effects with respect to number of estimated SERT sites in specific brain areas and performance on measures of memory. However, 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.

7.7. Adverse Events Outside of Sponsor-Supported Studies

MDMA was administered to thousands of people prior to scheduling and many continue to use ecstasy around the world in various non-medical settings [14-18]. While a number of serious adverse events, including fatalities, have been reported after ecstasy use in unsupervised and uncontrolled settings, these events are relatively rare given the prevalence of ecstasy use [19, 20]. These include hyperthermia, including hyperthermia arising from "serotonin syndrome," psychiatric problems, hepatotoxicity, including acute liver failure arising from hypethermia and liver disease and hyponatremia [19, 40, 213, 216, 343]. Unexpected drug-related serious adverse events have not occurred in any of the human MDMA research studies so far. Set and setting may play a role in the development of some ecstasy-related adverse events, such as rigorous exercise, lack of attention to somatic cues, and too little or too much hydration resulting in hyperthermia or hyponatremia [212]. Hall and Henry address medical emergencies related to ecstasy use [344]. 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 [216, 274, 345]. A very extensive and 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 [40]. As is the case with fatalities, medical emergencies after ecstasy use are more likely to occur in men [216].

Other infrequently reported serious adverse events reported in ecstasy users and reported in case reports or series, include cardiac problems (as arrhythmias) [230, 231, 346], cerebrovascular events (such as cerebral hemorrhage or infarction [222, 223, 347], dermatological (dermatitis, guttate rash [348]), dental (tooth erosion, likely from frequent bruxism) [349-351], hematological, including aplastic anemia [352, 353], respiratory (pneumomediastinum and subcutaneous emphysema) [354-357], ophthalmic (sixth nerve palsy, chorioretinopathy (a condition associated with sympathomimetic use), corneal epitheliopathy (resulting from corneal exposure produced by consuming CNS depressants) [358, 359] , urological (as urinary retention) events[360-362].

A large number of the case reports published between 2008 and 2012 described conditions and emergencies that have previously appeared in the literature. They included 12 cardiac events [363-368], three hepatic events (including a cardiac and hepatic event) [369-371], five cerebrovascular events[347, 372, 373], four psychiatric events [374-376], three instances of hyponatremia [377-379], three cases of rhabdomyolysis and/or hyperthermia [380-382], three neurological cases [383-385], and single reports of facial rash (eruption) [386], urinary retention

[360], rhabdomyolysis of masseter muscle [387], aplastic anemia [388] and fatal allergic reaction [389]. The cases reported 13 deaths[365, 367-369, 377, 379, 382, 388, 389] (7 after cardiac events, two after hyponatremia, one after liver disease, one after hyperthermia and rhabdomyolisis, one after aplastic anemia and one after apparent allergic reaction. The death after aplastic anemia occurred from complications of treatment 17 months after the first admission from complications arising from immunosuppressant therapy given after bone marrow transplant. Detectable levels of MDMA in blood or urine are reported in seven of the 31 case reports, and range from 50 ng/mL (reported as less than 0.05 mg/L) in the allergic reaction [389]to 1500 ng/mL (reported as 1.5 mg/L) in a fatal case of hyperthermia and rhabdomyolisis [382].Only one of three neurological events provided information on MDMA levels, 0.83 ng/mL detected in the hair of a girl who developed encephalopathy [384], with a course and symptoms that are similar to those seen after central nervous system herpes infection. It is more difficult to associate event with MDMA when the compound is not detected or when detection is for amphetamines in general. Some events, such as valvular heart disease, acute hepatitis with gallbladder inflammation, or urinary retention self-reported daily use for months to years prior to the event, The case of valvular heart disease occurred in an individual who indicated that he had taken ecstasy daily for approximately 16 years, from age 17 to 33 years old.

The report of possible anaphylactic shock occurred in a 13-year old girl who had at least one previous exposure to ecstasy. Her friends reported that she experienced swelling lips after the 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. None of the other individuals consuming tablets from the same batch underwent similar experiences. Autopsy found a massive brain edema as well as laryngeal edema and lung congestion. Chemical analyses ruled out hyponatremia. The reaction may have been to MDMA or to an adulterant in the tablet.

None of these events have occurred within the context of Phase 1 or Phase 2 human studies with MDMA.

7.8. Related Expected Adverse Events From Studies in Healthy Volunteers

Common expected adverse events of MDMA reported in Phase 1 studies in healthy volunteers include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils [3-6]. Some reports indicated decreased rather than increased alertness [3]. Other common adverse events reported in controlled studies of MDMA include reduced appetite, dizziness, tight jaw or bruxism (tooth-grinding), difficulty concentrating, 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 facilitated recall [8], and unusual thoughts or ideas [5]. Other less commonly reported events include parasthesias (unusual body sensations) such as tingling or feeling hot or cold. MDMA produces anxiety in healthy volunteers [5, 6, 8]. These effects are transient and recede with the waning of drug effects. 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 adverse events of nausea and sweating [6]. Adverse effects in women undergoing a single session of MDMA-assisted psychotherapy for PTSD were mild and appear to be similar to those in healthy controls [24].

Table 1: Acute Adverse events of MDMA Compiled from Literature of Human Trials with MDMA.

Data Source	**Prevalence Across Literature**		Downing 1986	Greer & Tolbert 1986	Vollenweider et al. 1998	Gamma et al. 2000	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Harris et. al. 2002	Bouso et. al. 2008	Hysek 2011	Hysek et. al. 2012a	Hysek et. al. 2012b
	Placebo	**MDMA**												
N:	10-57	6-174	**10**	**29**	**13**	**16**	**14**	**14**	**16**	**8**	**4**	**16**	**16**	**16**
MDMA Dose(s):	0	0.5-4.18 mg/kg	1.76-4.18 mg/kg	75-150, 200 mg	1.7 mg/kg	1.7 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	0.5, 1.5 mg/kg	50, 75 mg	125 mg	125 mg	125 mg
Time post-drug	-	-	2-5 hr	N/A	0-3 hr	N/A	N/A	N/A	N/A	0-24 hr	24 hr	0, 3, 24 hr	3, 24 hr	3, 24 hr
Lack of Appetite	2%	68%	100%	97%	62%	63%	50%	50%	50%	63%	N/A	75%	56%	69%
Dry Mouth	N/A	64%	N/A	N/A	N/A	N/A	57%	57%	N/A	88%	N/A	N/A	63%	N/A
Jaw Clenching	0%	60%	60%	76%	62%	64%	57%	71%	44%	N/A	N/A	N/A	44%	50%
Concentration Issues	16%	53%	30%	3%	62%	50%	71%	50%	63%	88%	25%	75%	N/A	N/A
Thirst	4%	48%	N/A	N/A	38%	50%	57%	57%	38%	N/A	N/A	N/A	N/A	63%
Restlessness	0%	46%	N/A	N/A	31%	N/A	50%	29%	44%	N/A	N/A	50%	44%	69%
Restless Legs	0%	45%	N/A	N/A	46%	N/A	N/A	N/A	44%	N/A	N/A	N/A	N/A	N/A
Impaired Balance/Gait	0%	44%	70%	10%	62%	N/A	71%	43%	50%	N/A	N/A	N/A	N/A	N/A
Dizziness	2%	43%	N/A	N/A	31%	N/A	57%	21%	50%	75%	N/A	38%	N/A	N/A
Feeling Cold	4%	43%	N/A	N/A	23%	N/A	43%	N/A	N/A	75%	N/A	N/A	N/A	N/A

Perspiration	0%	40%	N/A	N/A	0%	50%	36%	N/A	N/A	50%	N/A	N/A	50%	50%
Sensitivity to Cold	7%	38%	N/A	N/A	38%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Private Worries	23%	38%	N/A	N/A	38%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Heavy Legs	0%	38%	N/A	N/A	38%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Palpitations	0%	37%	N/A	N/A	31%	38%	43%	21%	N/A	63%	N/A	N/A	N/A	N/A
Drowsiness	50%	26%	N/A	14%	N/A	N/A	43%	N/A	N/A	N/A	50%	N/A	N/A	N/A
Data Source	**Prevalence** Across Literature		Downing 1986	Greer & Tolbert 1986	Vollenweider et al. 1998	Gamma et al. 2000	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Harris et. al. 2002	Bouso et. al. 2008	Hysek 2011	Hysek et. al. 2012a	Hysek et. al. 2012b
	Placebo	**MDMA**												
N:	10-57	6-174	**10**	**29**	**13**	**16**	**14**	**14**	**16**	**8**	**4**	**16**	**16**	**16**
MDMA Dose(s):	0	0.5-4.18 mg/kg	1.76-4.18 mg/kg	75-150, 200 mg	1.7 mg/kg	1.7 mg/kg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	0.5, 1.5 mg/kg	50, 75 mg	125 mg	125 mg	125 mg
Nystagmus	N/A	23%	80%	3%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hot Flashes	0%	23%	N/A	N/A	23%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nausea	4%	21%	10%	24%	8%	N/A	36%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Trismus	N/A	21%	N/A	3%	N/A	N/A	57%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Anxiety	0%	19%	N/A	17%	N/A	N/A	14%	N/A	N/A	N/A	50%	N/A	N/A	N/A
Inner Tension	0%	18%	N/A	3%	23%	N/A	43%	14%	19%	N/A	50%	N/A	N/A	N/A

Insomnia	0%	17%	0%	N/A	31%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weakness	0%	16%	N/A	3%	23%	N/A	36%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urge to Urinate	8%	15%	N/A	N/A	15%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tremor	0%	22%	N/A	3%	31%	N/A	21%	14%	N/A	N/A	N/A	56%	N/A	N/A
Muscle Ache/ Tension	N/A	20%	N/A	21%	0%	N/A	N/A	N/A	N/A	50%	N/A	N/A	N/A	N/A
Forgetfulness	0%	15%	N/A	3%	38%	N/A	N/A	N/A	N/A	N/A	25%	N/A	N/A	N/A
Fatigue	26%	15%	N/A	7%	8%	N/A	N/A	29%	N/A	N/A	50%	N/A	N/A	N/A
Parasthesias	0%	22%	N/A	3%	31%	N/A	N/A	N/A	N/A	75%	N/A	N/A	N/A	N/A
Lack of Energy	14%	14%	N/A	3%	N/A	N/A	29%	N/A	N/A	N/A	50%	N/A	N/A	N/A
Brooding	0%	12%	N/A	3%	N/A	N/A	29%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fainting	N/A	3%	N/A	3%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Blurred Vision	N/A	3%	N/A	3%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lip Swelling	N/A	2%	N/A	3%	0%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Headaches	N/A	11%	0%	3%	N/A	N/A	N/A	0%	N/A	50%	50%	N/A	N/A	N/A

8. Safety and Efficacy in Humans

In recent years, clinical investigation of the safety and efficacy of MDMA-assisted psychotherapy has become more feasible [390, 391]. The first double blind, placebo controlled, ascending dose U.S. Phase 1 study sanctioned by the FDA and supported by the Sponsor was conducted in 1994 [13, 202, 323]. In this study, MDMA was found to be generally tolerable in a clinical setting. These results lead to the first Phase 2 safety and efficacy study of low doses of MDMA-assisted psychotherapy in Spain on a small sample of women with chronic PTSD [24]. The study was originally approved for 29 subjects, but media and political pressure caused discontinuation of the study after only 6 subjects had been treated. The small sample size precluded statistical analysis for efficacy, yet the safety profile in the PTSD subject sample appeared promising as neither 50 nor 75 mg MDMA were found to increase psychopathological symptoms in this patient population. In July 2010, the Sponsor completed the first U.S. Phase 2 pilot study investigating the safety and efficacy of MDMA-assisted psychotherapy for patients with chronic treatment-resistant PTSD, protocol MP-1 [266]. Analysis of the results from this small pilot study from 21 subjects randomized to 125mg MDMA (N=13) or inactive placebo (N=8) suggest that MDMA-assisted psychotherapy can significantly decrease PTSD symptoms compared to placebo-assisted psychotherapy and appears to be safe when administered in a controlled therapeutic setting [266]. Findings from the long-term follow-up of MP-1 subjects suggest that therapeutic benefits were sustained over an average of 41 months post-treatment [22]. The Sponsor completed a second study in Switzerland, MP-2, with a randomized, active placebo controlled, double blind design. In this study, 12 subjects were randomized to receive 25mg or 125mg MDMA during three psychotherapy sessions (Oehen 2012). Results suggests clinically significant improvements in PTSD symptoms with a trend toward statistical significance [23]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. Additional phase studies are currently underway.

8.1. Safety of MDMA-assisted psychotherapy for PTSD

MP-1 enrolled 22 adult participants with PTSD with symptoms that failed to respond to at least one course of psychotherapy and at least one course of pharmacotherapy. An additional participant, a male veteran who refused prior treatment, was also enrolled after approval of an amendment by the FDA. The study enrolled eight women and five men, all were European-American, average age 40.6 years. Subjects enrolled had no history of major medical conditions, psychotic disorders, dissociative identity disorder, or personality disorders. Safety data obtained from this study included: scores from tests of cognitive function performed before and after study participation, vital signs and a measure of psychological distress during experimental sessions, expected adverse events for three experimental sessions, and adverse events that occurred during the study.

Two subjects (1 woman, 1 man) withdrew from the study after a single experimental session. The male subject withdrew from the study due to financial constraints on travel reimbursements, and the female subject withdrew from the study after experiencing a relapse of depression that required medication occurring 42 days after MDMA administration. Prior to relapse, the same subject had been hospitalized for benzodiazepine withdrawal while tapering medication. This subject reported reduction in PTSD symptoms even though the depression required medication.

There were no deaths during this study and no drug-related serious adverse events. Two unrelated, non-life threatening, serious adverse events occurred during the study. The first was a fractured clavicle from a vehicular accident in which the subject was a passenger, resulting in temporary disability and resolving with complete recovery. The second was an episode of vasovagal syncope, occurring 41 days after the second administration of MDMA and resolving with recovery to baseline. This subject had a medical history of fainting spells, and follow-up reports filed 15 months after the event indicate that it was not recurrent.

MP-2 enrolled fourteen adult participants (11 women, three men, average age 41.8 years) with PTSD with symptoms that failed to respond to at least one course of psychotherapy or pharmacotherapy. Most were of European ethnicity, but one woman was African and one man was Middle Eastern. Subjects enrolled had no psychotic disorders, dissociative identity disorder, or personality disorders. One subject had a previous history of breast cancer, but had been in remission for over 10 years and was not symptomatic at screening. Safety data obtained from this study included: vital signs and a measure of psychological distress during experimental sessions, expected adverse events for three to five experimental sessions, and adverse events that occurred during the study.

There were no serious drug-related adverse events in the MP-2 study. There was one death during the post-treatment follow-up period of the study from the metastasis of a brain tumor. The subject's death was the result of a previous condition and was determined to be unrelated to the study drug. There was one non-fatal, drug-unrelated serious adverse event that occurred during the study. A subject allegedly was hospitalized two weeks prior to administration of the study drug after exhibiting suicidal behavior following a conflict with her ex-husband. The subject was discharged from the hospital the next day, and did not exhibit suicidal or violent tendencies or any mental state requiring hospitalization prior to or after this event.

Two subjects (1 man, 1 woman) withdrew from the study as a result of adverse events occurring during the first experimental session. The first participant, who had received 125 mg MDMA experienced severe exacerbation of anxiety during the first experimental session. This event interrupted the experimental session and was treated with additional support during therapy until the drug effects dissipated. The anxiety was a part of PTSD symptoms present at baseline and its exacerbation was deemed to be probably related to drug administration. The second participant, who received 25 + 12.5 mg MDMA, experienced severe anxiety in reaction to being confronted with traumatic memories during the first experimental session, with the anxiety deemed possibly related to drug administration. The anxiety was treated with additional support in the form of therapy after the drug effects dissipated.

8.1.1. Vital signs

As expected, vital signs during experimental sessions indicate that MDMA elevates blood pressure and heart rate, but elevations return to baseline or near-baseline seven to eight hours after drug administration. Repeated measures analyses of variance using MP-1 average pre-drug, peak and final post-drug measurements of SBP, DBP, heart rate and body temperature after placebo versus MDMA detected significant interactions between measurement and dose for SBP ($F(1.71, 130 = 12.24, p < 0.000)$ and heart rate ($F(2, 130 = 13.01, p. < 0.000)$, and not for DBP

or body temperature. As expected, MDMA significantly elevated SBP and HR when compared with inactive placebo. By the end of the experimental session, SBP after MDM was 33 mm Hg lower than peak values, and HR was 20.47 BPM lower, indicating the return to pre-drug or near pre-drug levels. Analyses of MP-2 Stage 1 cardiovascular and body temperature measures found a main effect of condition for peak and post-drug average SBP, but one-way ANOVA failed to detect any main effect of condition for DBP, heart rate, or body temperature. Because MP-2 did not collect final measurement, the degree to which peak values returned to normal post-drug cannot be assessed in this sample. The addition of a supplemental dose of MDMA did not increase peak values for vital signs measured during experimental sessions.

Table 2a. : Pre-Drug, Peak, and Final SBP and DBP Values Measured During MP-1

Dose administered within session		SBP: Pre-Drug	SBP: Peak	SBP: Final	DBP: Pre-drug	DBP: Peak	DBP: Final
0 mg 16 sessions 8 subjects	Mean (SD)	112.3 (10.8)	127.7 (15.3)	108.8 (13.1)	73.5 (8.4)	84.6 (10.4)	69.4 (10.4)
	Peak	136.5	157.0	133.0	87.5	102.0	89.0
125 mg 25 sessions 14 subjects	Mean (SD)	111.9 (11.7)	144.7 (18.3)	112.5 (9.3)	72.2 (8.8)	88.6 (11.0)	71.1 (6.7)
	Peak	145.5	189.0	126.0	93.5	113.0	87.0
187.5 mg 26 sessions 10 subjects	Mean (SD)	122.6 (9.9)	151.0 (15.9)	116.7 (10.8)	79.7 (6.4)	93.7 (7.8)	76.2 (6.8)
	Peak	143.5	181.0	141.0	94.0	103.0	88.0

Table 2b. Pre-Drug, Peak, and Final HR and BT (C°) Values Measured During MP-1

Dose administered within session		HR: Pre-drug	HR: Peak	HR: Final	BT: Pre-drug	BT: Peak	BT: Final
0 mg 16 sessions 8 subjects	Mean (SD)	68.2 (10.2)	82.5 (9.6)	71.4 (8.4)	97.5 (0.9)	98.4 (0.6)	97.8 (0.6)
	Peak	91.0	107.0	89.0	99.0	99.6	98.6
125 mg 25 sessions 14 subjects	Mean (SD)	73.3 (11.5)	102.8 (15.0)	82.7 (10.0)	97.6 (0.7)	98.9 (0.5)	98.0 (0.7)
	Peak	99.5	135.0	104.0	99.6	100.0	99.4
187.5 mg 26 sessions 10 subjects	Mean (SD)	74.2 (13.0)	103.7 (19.1)	82.9 (15.7)	97.4 (0.9)	98.6 (0.9)	98.0 (0.7)
	Peak	95.0	140.0	119.0	99.1	100.1	99.3

Table 2c. Pre-Drug, Peak, and Final SBP and DBP Values Measured During MP-2

Dose administered within session		SBP: Pre-drug	SBP: Peak	SBP: Final	DBP: Pre-drug	DBP: Peak	DBP: Final
37.5 mg 13 sessions 5 subjects	Mean (SD)	119.5 (4.6)	131.3 (7.3)	115.9 (7.0)	76.3 (4.0)	84.8 (4.8)	74.5 (3.8)
	Peak	126	144	127	84	92	81
125 mg 3 sessions 2 subjects	Mean (SD)	142.0 (12.3)	181.3 (15.3)	155.3 (11.7)	90.3 (6.6)	110.3 (10.1)	95.7 (7.8)
	Peak	151	193	164	98	121	102
187.5 mg 36 sessions 12 subjects	Mean (SD)	129.9 (16.1)	154.4 (19.4)	135.4 (16.3)	80.0 (8.8)	92.8 (10.2)	81.4 (9.3)
	Peak	177	200	168	101	114	100
212.5 mg 2 sessions 2 subjects	Mean (SD)	132.0 (17.0)	170.5 (20.5)	148.5 (17.7)	83.0 (9.9)	103.5 (6.4)	87.5 (12.0)
	Peak	144	185	161	90	108	96
225 mg 2 sessions 2 subjects	Mean (SD)	124.0 (31.1)	142.5 (20.5)	133.5 (23.3)	74.5 (20.5)	87.0 (12.7)	76.5 (13.4)
	Peak	146	157	150	89	96	86

Table 2d. Pre-Drug, Peak, and Final HR and BT (C°) Values Measured During MP-2

Dose administered within session		HR: Pre-Drug	HR: Peak	HR: Final	BT: Pre-Drug	BT: Peak	BT: Final
37.5 mg 13 sessions 5 subjects	Mean (SD)	76.1 (9.8)	90.8 (18.1)	76.0 (10.9)	36.6 (0.2)	37.6 (0.5)	37.2 (0.4)
	Peak	94	124	90	37.1	38.5	38.00
125 mg 3 sessions 2 subjects	Mean (SD)	79.3 (2.9)	88.7 (15.3)	78.3 (10.6)	36.7 (0.5)	37.3 (0.2)	37.1 (0.2)
	Peak	81	98	88	37.1	37.5	37.30
187.5 mg 36 sessions 12 subjects	Mean (SD)	80.8 (10.4)	105.3 (15.3)	89.0 (12.2)	36.5 (0.4)	37.6 (0.6)	37.2 (0.4)
	Peak	109	144	116	37.6	38.7	38.40
212.5 mg 2 sessions 2 subjects	Mean (SD)	76.0 (1.4)	107.5 (0.7)	96.0 (4.2)	36.7 (0.1)	37.6 (0.4)	37.3 (0.6)
	Peak	77	108	99	36.7	37.9	37.68
225 mg 2 sessions 2 subjects	Mean (SD)	82.5 (19.1)	104.0 (29.7)	93.0 (26.9)	36.7 (0.1)	37.9 (0.5)	37.4 (0.2)
	Peak	96	125	112	36.7	38.2	37.54

8.1.2. Psychological Effects

Psychological distress of participants was assessed periodically throughout experimental sessions in both studies with the single-item, seven-point Subjective Units of Distress (SUD). In both studies, there was no significant difference in SUD scores between MDMA and placebo conditions. In MP-1, an analysis comparing pre-drug average, peak and final post-drug SUD ratings made by participants receiving MDMA versus placebo across Stage 1 and Stage 2 failed to find statistically significant differences in SUD scores. The interaction between dose given (placebo, MDMA) and pre-drug, peak and post-drug SUD was $F(2, 130) = 1.84$, $p. = 0.164$, and there was no main effect of dose (MDMA or placebo), $F(1, 65) = 1.16$, $p > 0.05$ ($p. = 0.29$). MDMA did not elevate psychological distress in participants with PTSD to a greater degree than for participants given placebo.

Table 3: Table : Subjective Units of Distress Measured in MP-1

	Dose given	Mean	Std. Dev.	N
Pre-drug	Placebo	3.72	1.97	16
	MDMA	3.05	1.81	51
	Total	3.21	1.85	67
Peak	Placebo	5.19	1.56	16
	MDMA	4.55	1.88	51
	Total	4.70	1.82	67
Final	Placebo	1.69	0.60	16
	MDMA	1.82	1.01	51
	Total	1.79	0.93	67

8.1.3. Expected Adverse Events

Spontaneously reported expected adverse events were collected during the day of each experimental session and for seven days after each session. The list of commonly expected adverse events was derived from the literature (see Table 1). Severity of spontaneously reported reactions were collected on the day of each experimental session and for up to seven days after the session through telephone or face to face contact, with severity rated on a three-point scale. The investigators collected information on duration of reaction for any reaction reported on the day of an experimental session. Anxiety, fatigue, tight jaw, headache, insomnia and lack of appetite were commonly listed during experimental sessions. Anxiety and fatigue were reported at near equal levels by participants given inactive or active placebo and MDMA, while reports of tight jaw were far more frequent in people who received a full dose of MDMA than people who received placebo. Feeling cold, while reported in only 38% of 35 people given a full dose of MDMA, was reported markedly less often in people given inactive or active placebo (19% and 15% respectively). Other less frequently reported reactions that appeared to occur more often in people given at least 125 mg MDMA included impaired gait or balance, impaired concentration and restlessness.

Table 4: Expected Adverse Events Reported for Studies MP-1 and MP-2

Study	**MP1**		**MP2**			**Total**			
MDMA Initial Dose (mg)	**0**	**125**	**25**	**125**	**150**	**0**	**25**	**125**	**150**
Number of Subjects	**8**	**22**	**5**	**13**	**3**	**8**	**5**	**35**	**3**
Number of Sessions	**16**	**51**	**13**	**39**	**4**	**16**	**13**	**90**	**4**
Psychiatric									
Anxiety	14(88%)	48(94%)	4(31%)	20(51%)	1(25%)	14(88%)	4(31%)	67(74%)	1(25%)
Low mood	8(50%)	16(31%)	7(54%)	20(51%)	1(25%)	8(50%)	7(54%)	35(39%)	1(25%)
Insomnia	12(75%)	32(63%)	9(69%)	24(62%)	3(75%)	12(75%)	9(69%)	55(61%)	3(75%)
Restlessness	2(13%)	10(20%)	0	17(44%)	1(25%)	2(13%)	0	24(27%)	1(25%)
Disturbance in attention	2(13%)	12(24%)	0	13(33%)	0	2(13%)	0	25(28%)	0
Drowsiness	3(19%)	4(8%)	1(8%)	3(8%)	0	3(19%)	1(8%)	7(8%)	0
Private Worries	2(13%)	6(12%)	3(23%)	10(26%)	0	2(13%)	3(23%)	15(17%)	0
Nervous System									
Headache	10(63%)	29(57%)	5(38%)	15(38%)	1(25%)	10(63%)	5(38%)	46(51%)	1(25%)
Dizziness	2(13%)	21(41%)	4(31%)	12(31%)	3(75%)	2(13%)	4(31%)	33(37%)	3(75%)
Gastrointestinal									
Nausea	4(25%)	25(49%)	3(23%)	11(28%)	1(25%)	4(25%)	3(23%)	35(39%)	1(25%)
General									
Fatigue	14(88%)	44(86%)	7(54%)	27(69%)	3(75%)	14(88%)	7(54%)	69(77%)	3(75%)
Dry Mouth	0	13(25%)	0	7(18%)	1(25%)	0	0	20(22%)	1(25%)
Heavy Legs	0	2(4%)	1(8%)	1(3%)	1(25%)	0	1(8%)	3(3%)	1(25%)
Impaired Balance	1(6%)	15(29%)	3(23%)	16(41%)	2(50%)	1(6%)	3(23%)	29(32%)	2(50%)
Irritability	8(50%)	18(35%)	1(8%)	9(23%)	0	8(50%)	1(8%)	26(29%)	0
Needs More Sleep	2(13%)	11(22%)	2(15%)	4(10%)	2(50%)	2(13%)	2(15%)	15(17%)	2(50%)
Nystagmus	0	8(16%)	0	4(10%)	1(25%)	0	0	12(13%)	1(25%)
Parasthesia	0	4(8%)	0	2(5%)	1(25%)	0	0	6(7%)	1(25%)
Perspiration	2(13%)	13(25%)	0	6(15%)	1(25%)	2(13%)	0	18(20%)	1(25%)
Feeling Cold	3(19%)	24(47%)	2(15%)	10(26%)	0	3(19%)	2(15%)	34(38%)	0
Thirstiness	1(6%)	7(14%)	0	10(26%)	0	1(6%)	0	17(19%)	0
Feeling Weak	1(6%)	10(20%)	0	5(13%)	1(25%)	1(6%)	0	15(17%)	1(25%)
Musculoskeletal & Connective Tissue									
Muscle tension	3(19%)	42(82%)	1(8%)	16(41%)	1(25%)	3(19%)	1(8%)	56(62%)	1(25%)
Metabolism and Nutrition									
Lack of appetite	1(6%)	33(65%)	6(46%)	17(44%)	1(25%)	1(6%)	6(46%)	43(48%)	1(25%)

8.1.4. Unexpected Adverse Events

One hundred eighty-six adverse events were reported as occurring during studies MP-1 and MP-2. A hundred and twenty-five unexpected adverse events were reported during study MP-1 and 61 unexpected AEs were reported during study MP2. This includes events that occurred prior to administration of medication but after study enrollment. The majority of these events were deemed unrelated (44% of 186 reported, or 81 events) and 34% (63%) were deemed to be possibly related. Twenty-three per cent (42 of 186) were rated as probably related. Since relationship was assessed when the investigator was blinded during Study MP1, some unexpected AEs that were deemed related to the study drug occurred in people given inactive placebo. The greatest number of AEs was reported in 29 of 35 people receiving a full dose (125 mg, with or without supplemental dose) (139 of 186). Fourteen AEs occurred in three of five people given 25 mg MDMA and 33 occurred in all eight people given placebo. Information on the number of unexpected AEs, relatedness, severity and AE outcome can be found in Tables 5a to 5c, below.

Table 5a. Presence and Frequency of Unexpected AEs in Studies MP-1 and MP-2

	Placebo	**25 mg**	**125 mg**	**Total**
Number of Subjects given dose	8	5#	35#**	
Any AEs	33	14	139	186
% of Unexpected AEs	18%	8%	75%	100%
At Least Possibly Related AEs	24*	4	77	105
% of all AEs within Dose	73%	29%	55%	100%
% of all Unexpected AEs	13%	2%	41%	56%
Serious AEs	0	0	4	4
% of all AEs within dose	0%	0%	3%	2%
% of all Unexpected AEs	0%	0%	2%	2%
At Least Possibly Related SAEs	0	0	0	0

*Relatedness rated while blinded
#Subjects withdrew prior to all three sessions, including 1 at 25 mg and three at 125 mg.
** Includes 24 at Stage 1 and 11 placebo or active placebo subjects at Stage 2
Combined table for MP1 and MP2

The intensity of most unexpected adverse events across both studies was rated as moderate. This was true for events in participants who received placebo and 125 mg MDMA. The equal percentage of moderate and severe AEs in participants given active placebo likely reflects the small number of events. Most subjects reported full recovery from these AEs, with 91% of AEs across placebo, 25 and 125 mg MDMA dose.

Table 5b. Severity of unexpected AEs from studies MP1 and MP2 listed by dose

AE Severity	**Placebo**	**%/all Placebo AEs**	**25 mg MDMA**	**%/all 25 mg MDMA AEs**	**125 mg MDMA**	**%/all 125 mg MDMA AEs**	**Total**	**%/all AEs**
Mild	5	15%	4	29%	43	31%	52	28%
Moderate	25	76%	5	36%	87	63%	117	63%
Severe	3	9%	5	36%	9	06%	17	9%
Total	33		14		139		186	

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Table 5c. All Studies Cumulative Severe Adverse Events
(Based on data received from the sites)

Study	Dose	Subject Number	Adverse Event Diagnosis	Date Last MDMA Admin.	Onset Date	Resolution Date	Serious	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relationship to Drug
MP-1	Placebo	0204	Re-experiencing episode	27-Aug-04	28-Aug-04	29-Aug-04	N	Single/ Intermittent	None	Other	Phone contact	Full recovery/ return to baseline	Possibly related
MP-1	Before dosing	0208	Agoraphobia	none	4-Apr-05	9-May-05	N	Continuous	Delayed exper-imental session	Hospital-ization	None	Full recovery/ return to baseline	Not related
MP-1	125mg MDMA	0208	Relapse of major depression	17-Jun-05	29-Jul-05	Ongoing at time of discontinuation	N	Continuous	Discon-tinued exper-imental session	Prescription med	Per her doctor	Persists, diminishing	Not related
MP-1	Before dosing	0208	Benzodiazepine withdrawal	none	4-Apr-05	9-May-05	N	Continuous	Delayed exper-imental session	Hospital-ization	None	Full recovery/ return to baseline	Not related
MP-1	125mg MDMA	0209	Sinusitis	22-Jul-05	12-Sep-05	22-Sep-05	N	Single/ Intermittent	None	Prescription med	None	Full recovery/ return to baseline	Not related
MP-1	Placebo	0212	Musculoskeletal chest pain	10-Mar-06	10-Mar-06	10-Mar-06	N	Single/ Intermittent	None	None	None	Full recovery/ return to baseline	Probably related

Unexpected adverse events across both studies were distributed across 19 of the 26 highest-level groups of MedDRA (System Organ Classes, or SOCs), and one that was not placed within any SOC (being the passenger in an automobile accident without reported injury). Most AEs fell under Psychiatric Disorders or General Disorders. From 24 to 43% all AEs fell within the Psychiatric Disorders SOC and included increased anxiety, panic attack, derealization and insomnia. AEs listed under general disorders included fatigue, feeling hot or cold, or body tension. Amount of psychiatric complaints were relatively equal throughout all conditions. It is interesting that increased reports of pain or tightness appeared with relatively greater frequency in people given placebo (30% of people given placebo versus 13% of people given full-dose MDMA; none in people given 25 mg MDMA).

Table 6a. Unexpected AEs by MedDRA System Organ Class listed by dose

MDMA Dose	0 mg			25 mg			125 mg			Total	
Body System	N	%/ Dose	%/ SOC	N	%/ Dose	%/ SOC	N	%/ Dose	%/ SOC	N	SOC/ AEs
No AE (N/subjects)	**0**			**2**	14%	25%	**6**	4%	75%	**8**	4%
Cardiac disorders	**0**			**0**			**2**	1%	100%	**2**	1%
Ear and Labyrinth Disorders	**0**			**1**	7%	100%	**0**			**1**	1%
Eye disorder	**0**			**0**			**4**	3%	100%	**4**	2%
Gastrointestinal Disorders	**2**	6%	10%	**0**			**18**	13%	90%	**20**	11%
General Disorders and Administration Site Conditions	**4**	12%	14%	**4**	29%	14%	**21**	15%	72%	**29**	16%
Infections and Infestations	**3**	9%	23%	**0**			**10**	7%	77%	**13**	7%
Injury, Poisonings and Procedural Complications	**0**			**0**			**1**	1%	100%	**1**	1%
Investigations	**0**			**0**			**2**	1%	100%	**2**	1%
Metabolism and Nutrition Disorders	**0**			**0**			**4**	3%	100%	**4**	2%
Musculoskeletal and Connective Tissue Disorders	**10**	30%	36%	**0**			**18**	13%	64%	**28**	15%
Neoplasms: Benign, Malignant and Unspecified	**0**			**0**			**1**	1%	100%	**1**	1%

MDMA Dose	0 mg			25 mg			125 mg			Total	
Body System	**N**	**%/ Dose**	**%/ SOC**	**N**	**%/ Dose**	**%/ SOC**	**N**	**%/ Dose**	**%/ SOC**	**N**	**SOC/ AEs**
Nervous System Disorders	**2**	6%	13%	**2**	14%	13%	**12**	9%	75%	**16**	9%
Psychiatric Disorders	**8**	24%	16%	**6**	43%	12%	**35**	25%	71%	**49**	26%
Renal and urinary disorders	**0**			**0**			**2**			**2**	1%
Reproductive system and breast disorders	**0**			**0**			**1**	1	100%	**1**	1%
Respiratory, Thoracic, and Mediastinal Disorders	**1**	3%	14%	**1**	7%	14%	**5**	4%	71%	**7**	4%
Skin and Subcutaneous Tissue Disorders	**2**	6%	67%	**0**			**1**	1%	33%	**3**	2%
Surgical and medical procedures	**0**			**0**			**1**	1	100%	**1**	1%
Vascular Disorders	**0**			**0**			**1**	1	100%	**1**	1%
Not in established SOC*	**1**	3%	100%	**0**			**0**			**1**	1%
Total of all AEs	**33**			**14**			**139**			**186**	

Full dose includes full dose administered in Stage 1 and Stage 2. A count of "No AEs" could occur in one or both stages.

Seven severe unexpected AEs rated as either possibly or probably related to the study drug occurred during Study MP-1 and Study MP-2. Four of seven events represented a psychiatric complaint or experience, such as a panic attack or an episode of re-experiencing. Full recovery followed all seven events. Upon unblinding it transpired that two of these events had occurred in subjects given inactive placebo; an episode of re-experiencing and musculoskeletal chest pain. The other events were a panic attack after 125 and 62.5 mg in Study MP1, distress after confronting traumatic memories after 25 mg, headache after 25 mg, anxiety and increase in PTSD symptoms after 125 mg and a panic attack after 125 mg. Onset of these events ranged from the day of an experimental session in four cases to seven days after an experimental session in one case. Two of the events from Study MP-2 led to withdrawal from the study for one participant in the active placebo condition and one in the full dose condition. More details about these events can be seen in Table 5c.

Table 6b. Cumulative Frequency of Severe Adverse Events by Relatedness for Studies MP-1 and MP-2

Adverse Event	**MP-1**		**MP-2**		**Total**	
Number of Subjects	23		14		37**	
Number of Experimental Sessions	67		52		119	
Relatedness	PR	NR	PR	NR	PR*	NR*
Psychiatric						
Re-experiencing episode	1				1(2%)	0
Panic Attack	1		1		2(4%)	0
Relapse of major depression		1			0	1(2%)
Anxiety, distress			2		2(4%)	0
Insomnia				2	0	2(4%)
Agoraphobia		1			0	1(2%)
Nervous System						
Headache			1		1(2%)	0
Sciatica		1			0	1(2%)
Gastrointestinal						
Abdominal Cramps/Pain				1	0	1(2%)
General						
Benzodiazepine withdrawal		1			0	1(2%)
Body Pain				1	0	1(2%)
Musculoskeletal & Connective Tissue						
Musculoskeletal chest pain	1				1(2%)	0
Infections and Infestations						
Sinusitis		1			0	1(2%)
Neoplasms						
Brain metastasis				1	0	1(2%)

* Note: PR = Possibly or Probably Related to drug, NR = Not Related to drug, in the opinion of the investigator prior to breaking blind.
** Note: Percentages were calculated based on number of subjects experiencing the AE. Each subject receives between 2 and 6 experimental sessions, depending on the study protocol and their condition assignment
** Based on final data analyzed from the sponsor database listings for completed studies, and preliminary data for ongoing studies

Table 6c. Frequency of Unexpected Adverse Events by Relatedness and by Dosage

Relatedness	**Placebo**	**25 mg MDMA**	**125 mg MDMA**	**Total**	**Relatedness /All AEs**
Unrelated	**9**	**10**	**62**	**81**	**44%**
% out of all Unrelated AEs	11%	12%	77%	100%	
% of AEs at listed dose	27%	71%	45%	44%	
Possibly Related	**21***	**4**	**38**	**63**	**34%**
% of all Possibly Related AEs	33%	6%	60%	100%	
% of all at listed dose	64%	29%	27%	34%	
Probably Related	**3***	**0**	**39**	**42**	**23%**
% of all Probably Related AEs	7%	0	93%	100%	
% of all at listed dose	9%	0	28%	23%	
Total	**33**	**14**	**139**	**186**	**100%**

*Assessment made while blinded

Table 6d. Frequency of Unexpected Adverse Events by Outcome and Condition

Outcome	**0 mg**	**%/ Out come**	**25 mg**	**%/ Out Come**	**125 mg**	**% Out Come**	**Total**	**%/All Unexpec ted AEs**
Full Recovery	30	18%	12	7%	127	75%	169	91%
Persists, Diminishing	1	8%	2	17%	9	75%	12	6%
Persists, the Same	2	67%	0	0%	1	33%	3	2%
Persists, Worsening	0	0%	0	0%	1	100%	1	0.05%
Death	0	0%	0	0%	1	100%	1	0.05%

* Lists number of events and percentage of each dose category that makes up each outcome and for outcome totals, percentage of each outcome within all unexpected adverse events

Four serious adverse events occurred, two in study MP1 and two in study MP2. None of them were drug related. These included broken clavicle, syncope, frontal lobe syndrome, later discerned to be the result of tumor metastasis, and psychiatric hospitalization after self-harm. See table 6e for details of SAEs.

Table 6e. All Studies Cumulative Serious Adverse Events Occurring in Studies MP-1 and MP-2

Study	Dose	Subject Number	Adverse Event Diagnosis	Date Last MDMA Admin.	Onset Date	Resolution Date	Severity	Frequency	Action Taken for Study	Action Taken-Treatment	Action Taken Other	Outcome	Relationship to Drug
MP-1	125mg MDMA	0203	Fractured Clavicle (Auto Accident)	20-Aug-04	31-Aug-04	Continuing	Moderate	Single/ Intermittent	None	Other	Treated in ER	Persists, diminishing	Not related
MP-1	125mg MDMA	0209	Vasovagal Syncope	22-Jul-05	1-Sep-05	1-Sep-05	Moderate	Single/ Intermittent	None	Other	Evaluated in the ER	Full recovery/ return to baseline	Not related
MP-2	125mg MDMA	0101	Brain metastasis (Frontal brain syndrome)	4-Jan-07	31-May-07	18-Jul-07	Severe	Continuous	Removed from study	Hospital-ization	None	Death	Not related
MP-2	Before dosing	0103	Psychiatric hospitalization	none	20-Feb-07	21-Feb-07	Moderate	Single/ Intermittent	None	None	None	Full recovery/ return to baseline	Not related

One death occurred in study MP2. A participant with a previous history of breast cancer assigned to the MDMA condition had a tumor that had metastasized to the brain.

Table 6f. Other significant unexpected adverse events reported during Studies MP-1 and MP-2, including events that led to participant withdrawal

Study	Dose (mg)	Subject	Date of Last Drug Admin	MedDRA Lower Level term	Onset date	Resolution date	Action taken-treatment	Severity	Outcome	Relatedness
MP1	125 mg MDMA	208	17-Jun-2005	Major depression	29-July-2005	None listed	Prescription medication	Severe	Persists, diminishing	Unrelated
MP2	125 mg MDMA	101	24-Nov-06	Panic Attack	26-Nov-06	26-Nov-06	Prescription Medication	Moderate	Full Recovery	Possibly Related
MP2	125 mg MDMA	101	4-Jan-07	Panic Attack	6-Jan-07	6-Jan-07	Prescription Medication	Severe	Full Recovery	Possibly Related
MP2	125 mg MDMA	105	6-Sep-07	Exacerbation of anxiety	6-Sep-07	19-Sep-07	Withdrawn from study due to AE, Prescription Med	Severe	Persists, Diminishing	Probably Related
MP2	37.5 mg MDMA	105	13-Mar-08	Anxiety reaction	13-Mar-08	UNK-Apr-08	Prescription Medication, therapy	Severe	Full Recovery	Possibly Related

8.1.5. Cognitive Effects

An independent rater blind to study condition assessed cognitive performance in all participants at baseline and two months after the second experimental session, using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [392], the Paced Auditory Serial Addition and Subtraction Task (PASAT) [393, 394], and the Rey Osterreith figure [395]. The RBANS is a relatively short series of tests used to examine cognitive function. It yields a total score and five sub-scales, including memory, visual spatial, language, attention, and delayed memory, and the PASAT requires participants to add or subtract whole numbers (integers) as they are spoken by a recorded voice. Analyses examined RBANS total scores, percentile scores for PASAT Trial 1 and Trial 2, and X score for the Rey-Osterreith Figure. After establishing that participants in the MDMA and the placebo group performed similarly at baseline using an independent t-test, analyses comparing performance two months after the second experimental session also failed to find either improved or impaired cognitive function participants in the MDMA condition compared with participants in the placebo condition, suggesting that MDMA given during psychotherapy did not adversely affect cognitive function. There was no statistically significant difference between total RBANS scores obtained by participants given MDMA versus those given placebo at two-month follow up, as shown in a comparison of the difference between two-month follow up and baseline total RBANS score $t(1, 19) = 1.32$, $p > 0.05$ ($p = 0.2$). A comparison of the difference between two-month follow up and baseline PASAT scores for both trials failed to find significant differences in performance between participants in the MDMA and the placebo condition, including performance on trial one (t, (1, 19) = -0.211, $p > 0.05$ [p. = 0.83] and trial 2 (t, (1, 18) = 1.2, $p > 0.05$ [p. = 0.244]. The difference between two-month follow up and baseline performance on 30-second delay component of the Rey-Osterreith figure, a measure of delayed visual recall and design reproduction, was compared after MDMA and placebo. The analysis did not detect significant differences between MDMA and placebo participants on 30-second delay performance; 30-second delay raw score t (1, 18 = 1.024, p. > 0.05 [p. = 0.319], 30-second delay T score, t (1, 17)

= 1.115, p > 0.05 [p. = 0.281], and Centile score t (1, 16) = 0.543, p > 0.05 [p. = 0.595]. Taken together, these tests indicate a lack of effect of MDMA upon cognitive function in this study.

Table 8a. Neurocognitive Function - RBANS Total Scores at Baseline and Two Months after the Second Experimental Session

Condition	RBANS Total Score*: Baseline		RBANS Total Score*: 2-month follow up	
	Mean	SD	Mean	SD
Placebo (N = 8)	97.50	12.66	104.88	12.10
MDMA (N = 13)	107.85	13.48	109.00	10.80

*Higher scores indicate greater cognitive function

Table 8b. Cognitive Function - PASAT Trial 1 and Trial 2 Percentile Scores Baseline and Two months Post Follow Up

Condition	PASAT Trial 1 Baseline		PASAT Trial 1 2 month follow up		PASAT Trial 2 Baseline		PASAT Trial 2 2-month follow up	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Placebo (N = 8)	30.50	34.45	34.25	32.92	38.24	36.02	46.25	34.01
MDMA (N = 13)*	46.85	29.12	34.46	26.72	59.54	27.56	44.33	24.89

*N = 12 for Trial 2 at two-month follow up, as one person did not complete task.

Table 8c. Table 7c: Cognitive Function Rey Osterreith Completion at Thirty Seconds Delay at Baseline and Two Month Follow-Up

Condition	30 Second Delay: Baseline		30 Second Delay: 2-month follow up	
	Mean	SD	Mean	SD
Placebo (N = 8)	39.50	9.15	42.88	6.22
MDMA (N = 13*)	40.75	12.97	48.17	11.04

*Data for one subject is missing at Baseline

8.2. Efficacy of MDMA-assisted psychotherapy for PTSD

8.2.1. MP-1 Efficacy Results

Analyses of the Clinician Administered PTSD Scale (CAPS) [396, 397] prior to and after two experimental sessions found lower global scores, reflecting fewer or less intense PTSD symptoms, after undergoing experimental psychotherapy sessions with MDMA or placebo. In addition, participants in the MDMA condition experienced a greater decline in PTSD symptoms after undergoing experimental sessions than did participants in the placebo condition. Global CAPS scores declined for all participants over time (overall baseline mean Global CAPS = 79.1 +/- 21.7, and two months after the second experimental session, mean Global CAPS = 38.2 +/-

30.3), indicating a drop of 40.9 points, and a 52% reduction in symptoms. People in the MDMA and placebo conditions began the study with similar CAPS scores, while CAPS scores after experimental sessions were lower for people in the MDMA condition up through two months after the second experimental session (Placebo = 59.1 +/-28.9 versus MDMA, 25.4 +/- 23.95). Placebo participant scores dropped 20.5 points two months after the second experimental session while MDMA participant CAPS scores dropped 53.3 points, or a 26% drop in PTSD symptoms for controls versus a 68% drop in PTSD symptoms for MDMA participants.

Table 8a. Global CAPS Scores for Placebo and MDMA Subjects for MP-1 at T0 (baseline), T1 (p**ost-Session 1), T2 (post-Session 2), and T3 (2 months post-Session 2)**

Condition	T0*	T1	T2	T3
Placebo (n = 8)				
Mean (SD)	79.6 (22.0)	74.1 (28.5)	66.8 (27.0)	59.1 (28.9)
Range	54-111	21-105	22-103	14-86
MDMA (n = 13)				
Mean (SD)	79.7 (21.0)	36.4 (28.6)	29.2 (18.6)	25.39 (24.0)
Range	43-113	6-107	2-59	0-79
Total (n = 21)				
Mean (SD)	79.7 (20.8)	50.8 (33.6)	43.5 (28.5)	38.2 (30.3)
Range	43-113	6-107	2-103	0-86

*Dropout baseline scores excluded

At baseline, overall Impact of Events Scale scores were similar across both conditions (45.12 +/- 11.84 for placebo, 45 +/- 16.1 for MDMA). As with the CAPS, there was an overall decline in IES scores in participants in both groups two months after a second experimental session (from 45.05 +/- 14.3 at baseline to 212.625 +/- 18.4), or a 232.458-point decline in PTSD symptoms (520% decline). Participants who received MDMA had scores of 15.31 +/- 15.2, representing a 64% decline in PTSD symptoms (28.92 point decline) at two month follow up and participants that received placebo had 32.0 +/- 20.8, representing a 30% decline in symptoms (13.62 point drop). Two months after two sessions of MDMA-assisted psychotherapy, participants who received MDMA had scores of 16.08 +/- 15.6, representing a 64% decline in PTSD symptoms (28.92 point decline) and participants that received placebo had 31.5 +/- 19.3, representing a 30% decline in symptoms (13.62 point drop).

Five participants in the MDMA condition who received an additional session of MDMA-assisted psychotherapy experienced an additional decline in PTSD symptoms, with a global CAPS score of 17, (an 8.5 point decline) below the score seen two months after two sessions of MDMA-assisted psychotherapy under blinded conditions. For participants in the placebo condition, taking part in the open-label study continuation ("Stage 2") produced a Global CAPS of 33.86 (N = 7), a 31.7 point drop in global CAPS (43% decline in PTSD symptoms).

Table 8b. Table 8b: CAPS Scores for Stage 2 (Open-Label) at T3 (Post-Stage 1 Session 3), T4 (2 months post-Stage 2 Session 2), and T5 (2 months post-Stage 3 Session 3)

	T3	T4	T5
N	5	7	4
Mean (SD)	17.0 (15.8)	33.9 (12.8)	25.75 (7.0)
Range	0-36	15-49	19-34

At baseline, overall Impact of Events Scale scores were similar across both conditions (45.12 +/- 11.84 for placebo, 45 +/- 16.1 for MDMA). As with the CAPS, there was an overall decline in IES scores in participants in both groups two months after two experimental sessions (from 45.05 +/- 14.3 at baseline to 22.25 +/- 18.4), or a 22.8-point decline in PTSD symptoms (50% decline). Two months after two sessions of MDMA-assisted psychotherapy, participants who received MDMA had scores of 16.08 +/- 15.6, representing a 64% decline in PTSD symptoms (28.92 point decline) and participants that received placebo had 31.5 +/- 19.3, representing a 30% decline in symptoms (13.62 point drop).

Long-term follow-up data was collected for 20 participants of MP-1 [398]247, which was not statistically different from the mean CAPS score obtained two months after the second stage 1 or stage 2 experimental session (23.924.6; only includes the 17 participants who completed CAPS at LTFU) reported at the 2-month final outcome. The mean IES score at LTFU was 212.194, which was also not statistically different from the mean IES score (13.1919.8) reported at the 2-month final outcome. On the LTFU questionnaire, all subjects reported a benefit from participating in the study, with at least some benefit persisting.

Table 8c. Table 8c: CAPS Scores at LTFU

	Originally MDMA	Originally Placebo	MDMA and Placebo
N	11	6	17
Mean (SD)	25.7 (27.1)	18.7 (7.6)	23.2 (22.1)
Range	0-91	10-31	0-91

At the time of enrollment, 16 of 19 participants reached at LTFU (84%) of subjects were in active psychotherapy, with 12 of 19 (58%) taking psychiatric medications. At LTFU, only 98 of 19 (42%) were in psychotherapy, five of whom were receiving a different type of psychotherapy or psychotherapy from a different therapist. Only one participant not in psychotherapy just prior to the study was attending psychotherapy at LTFU. The percentage of subjects taking psychiatric medication did not change (12/19; 58%), but the mean number of medicines taken fell from 1.7 to 1.3. In addition, none of the medications taken at time of LTFU were for treatment of PTSD.

Table 8d. Table 8d: Medication and Psychotherapy Data Reported at LTFU

	Entry (**n=19**)	LTFU (**n=19**)
# taking meds	12	12
% taking meds	58%	58%
# taking meds for PTSD	7	0
Total # meds	32	23
Avg # meds	1.7	1.3
	Entry (**n=20**)	LTFU (**n=20**)
In therapy	17	9

These findings are suggestive of an effect of MDMA in combination with psychotherapy in reducing PTSD symptoms. The long-term follow-up findings further suggest that the benefits of MDMA-assisted psychotherapy for PTSD are enduring. The greatest problem in study interpretation is that the blind was not very effective, with most participants correctly guessing condition assignment and the investigators correctly guessing in all cases. However, the blind was effective for the independent rater, who was not present during therapy sessions and did not know people's guesses concerning their condition.

8.2.2. MP-2 Efficacy Results

The MP-2 study found results similar to the MP-1 study, but results were less marked. Analyses of global CAPS scores prior to and after three experimental sessions found lower global scores after undergoing experimental psychotherapy sessions with 125 mg MDMA, but not with a 25 mg MDMA active placebo. Global CAPS scores declined over time for the eight participants given a full dose of MDMA (overall baseline mean Global CAPS = 66.4 +/- 13.6, and three weeks after the third experimental session, mean Global CAPS = 50.7 +/- 19.7), indicating a drop of 15.7 points, or a 23.5% decrease in scores. On the other hand, global CAPS scores increased slightly over time for the four participants given an active placebo (overall baseline mean Global CAPS = 63.2 +/- 7.9, and three weeks after the third experimental session, mean Global CAPS = 66.5 +/- 7.5), indicating an increase of 2.3 points, or a 5.2% increase in CAPS scores.

Table 8e. MP-2 Stage 1 Mean CAPS Scores at T0 (Baseline), T1 (3 weeks post-Session 2), and T2 (3 weeks post-Session 3)

Condition assignment		**T0**	**T1**	**T2**
25 mg MDMA	N Mean (SD) Range	5 64.8 (7.7) 54-72	4 60.0 (6.8) 50-65	4 66.5 (7.6) 57-75
125 mg MDMA	N Mean (SD) Range	9 68.6 (14.3) 48-86	8 63.0 (17.8) 30-85	8 50.8 (19.7) 14-74
Total	N Mean (SD) Range	14 67.2 (12.1) 48-86	12 62.0 (14.7) 30-85	12 56.0 (17.9) 14-75

All four active placebo subjects continued to Stage 2 of the study and received open-label full dose MDMA. These subjects experienced a distinct decrease in PTSD symptom severity (at end of Stage 1, mean global CAPS = 66.5 +/- 7.5, and at end of Stage 2, mean global CAPS = 43.7 +/- 14.1).

Table 8f. MP-2 Stage 2 Mean CAPS Scores at T3 (3 weeks post-Session 2), T4 (3 weeks post-Session 3), and T5 (2 months post-Session 3)

Condition assignment		T3	T4	T5
25 mg MDMA (receiving 125 mg in Stage 2)	N Mean (SD) Range	4 42.5 (25.3) 11-64	4 43.8 (14.1) 25-56	4 36.8 (13.6) 21-50

Twelve participants were assessed 2 months after their final Stage 1 or Stage 2 experimental session, three participants were assessed 6 months after their final Stage 1 or Stage 2 experimental session, and ten participants were assessed 12 months after their final Stage 1 or Stage 2 session. From the 2-month follow-up, after receiving full dose MDMA in either Stage 1 or Stage 2, CAPS Global scores had dropped from an average of 45.0 +/- 16.4 (N=12) to 33.9 +/- 16.8 (N=10) at 12 months after final session. These data suggest that subjects may retain the benefits they experienced three weeks after their third full dose MDMA session, and they may continue to improve after finishing the treatment portion of the study. However, caution should be used in interpreting these results, as many subjects resumed concomitant therapy during the follow-up.

Table 8g. MP-2 Mean CAPS Scores at T6 (2 months follow-up post-Stage 1 or Stage 2), T7 (6 months follow-up), and T8 (12 months follow-up)

Condition assignment		T6	T7	T8
25 mg MDMA	N	4	1	4
	Mean (SD)	36.8 (13.6)	21.0	31.5 (19.2)
	Range	21-50	21	11-54
125 mg MDMA	N	8	2	6
	Mean (SD)	49.1 (16.8)	62.5 (3.5)	35.5 (16.8)
	Range	27-75	61-66	8-54
Total	N	12	3	10
	Mean (SD)	45.0 (16.4)	49.3 (24.7)	33.9 (16.8)
	Range	21-75	21-66	8-54

Though they do not represent as strong an effect of MDMA-assisted psychotherapy upon PTSD symptoms as findings from the MP-1 study, findings from the MP-2 study suggest that MDMA in combination with psychotherapy can reduce PTSD symptoms. The two studies differed with respect to sample size and location and placebo comparator, with MP-1 employing an inactive placebo while MP-2 employed 25 mg MDMA as an active placebo, resulting in somewhat greater success in maintaining the study blind.

Efficacy findings from both studies suggest that people with PTSD could benefit from a course of two or three sessions of MDMA-assisted psychotherapy.

8.3. Marketing Experience

MDMA is currently not approved for marketing anywhere in the world and is a Schedule 1 controlled substance in the U.S.

9. Summary of Data and Guidance for the Investigator

MDMA is a psychoactive compound that some researchers refer to as an entactogen, a compound that affects mood and perception and increasing prosocial feelings. On the basis of narrative reports and several initial studies of MDMA in psychotherapy, the sponsor is investigating use of this compound in combination with psychotherapy for people with PTSD.

Researchers have conducted *in vitro* and *in vivo* studies with MDMA, and clinical trials have been conducted in humans. MDMA is listed in the most restrictive drug schedule in the U.S. (Schedule 1) and is not permitted for use outside of research settings.

9.1. Pharmacology

The pharmacology of MDMA is complex and the chief mechanism behind its therapeutic effects is currently under investigation. Studies in rodents and cell cultures find that MDMA primarily releases serotonin, along with some norepinephrine and even less dopamine. This activity is probably through direct interaction with the transporters for each neurotransmitter. It also acts as an uptake inhibitor of serotonin, norepinephrine, and dopamine. MDMA has very little direct activity on postsynaptic neurotransmitter receptors, and most effects of MDMA are likely due to the direct and indirect effects of monoamine release. Indirect but potentially significant effects of MDMA include the release of the hormones oxytocin and prolactin and transient immunosuppressive and anti-inflammatory effects. Potentially therapeutic effects, such as increased feelings of closeness to others and specific changes in ability to detect facial emotion expression, may be tied to elevated oxytocin after MDMA. One study reported that blocking activation of 5HT2A receptors, but blockage of 5HT1A receptors, attenuated the mood-boosting effects of MDMA. Increased sociability and preclinical studies suggest that the MDMA enantiomers R-(-)-MDMA and S-(+)-MDMA produce different physiological and apparent subjective effects, but comparisons of MDMA enantiomers have not yet occurred in humans.

MDMA shares some effects with psychostimulants, such as increased energy, positive mood, increased blood pressure, heart rate, and it shares other effects with hallucinogenic (psychedelic) compounds, such as changes in perception and thinking, including perceived changes in meaning given to perception, facilitated imagination, and recall. Most previous research in rodents and primates used doses that are higher than those used in humans, and reported increased locomotor activity and signs of serotonin syndrome including flat body posture, an erect tail, forepaw treading and hyperactivity. Studies using approximately human equivalent doses do not report great increases in locomotion.

In humans, MDMA elevates positive mood, and may produce positively or negatively experienced derealization, increased vigor, and anxiety, and slight changes in perception. Recent reports suggest that it may also cause increased feelings of friendliness and sociability. Acutely, MDMA transiently and selectively affects performance on tasks requiring attention and memory. Studies investigating the impact of MDMA on driving suggest that the drug does not strongly alter driving, but impairs some driving-related skills.

MDMA is administered orally in all investigations in humans to date. In humans, onset of effects occurs approximately 30 to 60 minutes after administration, and peak effects occur 75 to 120 minutes after oral administration. Duration of effects lasts three to six hours. Orally administered MDMA has a half-life of seven to nine hours in humans and approximately three hours in monkeys. MDMA is metabolized in the liver by several enzymes. It is likely that active doses of MDMA saturate CYP2D6 function for an extended period, with function normalizing up to ten days post-MDMA. The enzymes CYP1A2, COMT and monoamine oxidase (MAO) may also be involved in the metabolism of MDMA.

Because of its activity as a monoamine releaser, MDMA administration is contraindicated in participants requiring medication with MAO inhibitors. 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.

9.2. Risks

Psychotherapists in the US began to use MDMA as an adjunct to psychotherapy in the mid to late 1970s, and a number of narrative accounts exist of therapeutic use prior to its scheduling. MDMA was administered to thousands of people prior to scheduling, and as of November, 2012, it has been administered to approximately 811 people. MDMA has been administered in early open-label studies as well as blinded, placebo controlled Phase 1 studies conducted in the US, Switzerland, Spain, the Netherlands, and the UK, and sponsor-supported studies of MDMA-assisted psychotherapy in the US, Switzerland and Israel. Two sponsor-supported studies have completed investigations of MDMA-assisted psychotherapy in people with PTSD, and another study was designed to investigate MDMA-assisted psychotherapy in people with advanced stage cancer. These studies have demonstrated that MDMA can be safely administered to people with PTSD in a clinical setting.

9.2.1. Risks Associated with Eligibility Screening

Investigators must establish participant eligibility prior to enrollment in trials with MDMA, with eligibility established through medical history, physical examination, vital signs, clinical laboratory tests, stress ECG (if indicated), psychiatric interview, and assessment of relevant psychiatric symptoms. Additional procedures may be used as required, such as exercise tests and ultrasound imaging. If the study is investigating use of MDMA in people with a specific psychiatric condition, then the investigators must also determine whether an individual has the condition. Submitting to a full medical examination may be time consuming and may be distressing or uncomfortable for some.

Prior to enrollment, blood will be drawn as part of screening to assessing eligibility. Temporary discomfort may arise as a result of sampling blood. Participants may experience temporary discomfort at the blood-draw site. There is also a remote possibility of inflammation or infection at the blood-draw site.

Studies of subjective effects of MDMA will employ measures of self-reported mood, experience, and emotional closeness to others. History, presence, and severity of psychiatric disorders are assessed via psychiatric interview and validated instruments such as the Structured Clinical Interview for Diagnosis (SCID) and the CAPS, to assess specific conditions. Because these interviews require individuals to discuss their condition, they may prove upsetting for some. These measures are expected to produce minimal discomfort. Investigators should be experienced in treating the condition under investigation and they should seek to minimize anxiety and distress during these interviews.

9.2.2. Risks Associated with Psychotherapy

Participants enrolled in studies of MDMA-assisted psychotherapy will have a moderate course of psychotherapy sessions with a pair of investigators, one male and one female. During both non-drug and MDMA-assisted psychotherapy sessions, participants will be asked to think about and discuss their experiences, thoughts, and emotions relating to their condition. They may experience intense emotional responses to recalling and speaking about this material. Even in a therapeutic context, thinking about and discussing traumatic experiences, symptoms related to the trauma or the effects of PTSD on life function can produce distress during and immediately after non-drug psychotherapy and experimental sessions. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable, and is considered a necessary part of the therapeutic process that requires proper facilitation and support from the therapists. Discontinuing PTSD medications and the acute and sub-acute effects of MDMA-assisted psychotherapy can produce shifts in mood and activation, which may increase likelihood of suicidal ideation or behavior.

The sponsor will record all psychotherapy sessions to audio and video, and participants may have access to recordings if they request them. The recordings will be used for further development of a manualized form of MDMA-assisted psychotherapy to be used in future research and to assess investigator adherence to any standardized treatment. Participants will receive information on who will have access to any of their recordings and will have control over any presentation of this material beyond viewing by investigators, trainees, or regulatory agencies. Permission for the recording is part of the informed consent.

9.2.3. Risks of MDMA

The toxicity of MDMA has been investigated in numerous animal and *in vitro* studies published in peer-reviewed journals. In addition, hundreds of published case reports describe adverse events in illicit ecstasy users. Serious MDMA toxicity is rare even in uncontrolled settings, where people take material of unknown identity, potency, and purity, and the many users consuming estimated MDMA doses that are several times higher than those used in the proposed program, without apparent toxicity. Hyperthermia is the most frequently reported adverse effect to occur in this population. In addition to hyperthermic syndromes, other rare adverse events include dysphoria, panic or psychotic response, hepatotoxicity, and hyponatremia. The majority of ecstasy users visiting emergency departments do so because of anxiety or panic. In human clinical trials using MDMA, restrictions in study eligibility are intended to reduce the likelihood of serious adverse events.

Most clinical trials of MDMA employ doses between 75 and 140 mg (1 to 2 mg/kg), comparing these doses with inactive placebo, lower doses of MDMA, or other compounds, such as methylphenidate (Ritalin). Sponsor-supported studies employ a standard full dose of 125 mg, possibly followed by a dose of 62.5 mg 1.5 to 2.5 hours later. A few studies have investigated repeated doses, with doses ranging from 75 and 50 mg to two doses of 100 mg MDMA. Earlier investigations administered the supplemental dose at 2 to 2.5 hours later. This dose has been

compared with doses of 25 mg and 12.5 mg MDMA, with more recent planned studies also employing 30 mg, 40 mg and 75 mg MDMA as comparison doses. All doses are orally administered in opaque capsules. Lactose or a similar inactive material will be used to ensure that all capsules are of equivalent weight and appearance.

Adverse events of MDMA are modest and generally have not been associated with serious discomfort by healthy volunteers in previous studies. Commonly reported adverse events of MDMA include tight jaw, loss of appetite, difficulty concentrating, and impaired gait or balance. Sub-acute effects, including fatigue, feeling anxious or weak, or experiencing low mood are reported up to three days after MDMA administration.

9.2.4. Neurological Risks

Extensive studies in animals suggest that high or repeated doses of MDMA can damage serotonergic axons originating in the brainstem dorsal raphe nuclei, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin, serotonin metabolites, and serotonin transporter site densities. While these findings are consistent across studies, these studies generally overestimated the human equivalence of the doses. Some researchers believe that MDMA is neurotoxic in humans even at doses used in clinical trials. However, studies in very moderate ecstasy users do not report an increase in a biological marker of neuronal injury, and only one of three studies of this marker in humans detected it in heavy users. Three recent retrospective studies found changes in 5HT2A receptors in moderate to heavy ecstasy users. Many retrospective studies have found that ecstasy users have fewer estimated serotonin transporter sites when compared with non-ecstasy users, though some have failed to detect differences. Retrospective studies have also found impaired performance of measures of verbal memory, planning and making decisions, and visual memory. However, some retrospective studies have found little or no differences in cognitive function. A team in the Netherlands has conducted a prospective study of people prior to and after moderate use of ecstasy (in most cases 1-6 tablets). They failed to find changes in serotonin transporter sites or signs of neuronal injury. They found slight changes in cerebral blood flow in the dorsolateral prefrontal cortex but nowhere else. They did find that ecstasy users showed less improvement on a memory task than non-users. It is notable that the study examining SERT sites and regional cerebral blood flow did not employ non-ecstasy user controls, that all participants in the study of cognitive function performed within the normal range, and that one individual examined in the study of cognitive function had reportedly used ecstasy on 30 occasions rather than the limit of 10 occasions set for the other subjects. Data from MP-1, described previously, failed to find differences in neurocognitive performance between people given MDMA and people given inactive placebo. Taken together, these findings fail to confirm serotonergic neurotoxicity after low ecstasy use, but do suggest possible indications of impaired memory.

9.2.5. Cardiovascular Risks

The full dose of 125 mg, alone or followed by a supplemental dose of 62.5 mg 1.5 to 2.5 hours later, is expected to produce significant but transient, self-limited increases in blood pressure and heart rate. Participants enrolled in controlled trials with a single dose of MDMA (approximately 5% per trial) have had elevations above a cut-off of at least 140/90 mmHg, while all participants given a regimen of 100 mg followed by 50 mg two hours later had elevations above 140/90.

Systolic blood pressure above 160 mmHg was detected in approximately 20% to 30% of participants with PTSD, and diastolic blood pressure greater than 110 mmHg occurred in approximately 7% to 10% of participants with PTSD. No medical intervention was needed in studies of healthy humans or people with PTSD. Tables XX to YY show the degree of increase in vital-sign measurements in the investigators' recently completed clinical trial. While maximum peak blood pressure during a given session in some cases rose above the cut-off for making more frequent measures (160 Systolic Blood Pressure (SBP) or 110 Diastolic Blood Pressure (DBP)), no subjects in MP-1 or other clinical trials using MDMA have required any clinical interventions for elevated blood pressure or pulse, and all values returned to normal as the effects of MDMA diminished. The degree of additional blood pressure and pulse elevation is minimal after a second dose of MDMA half the original dose given 1.5 to 2.5 hours after the first dose.

Data from MP-1 demonstrates that elevation in blood pressure and heart rate after the supplemental dose does not exceed elevations seen after the initial dose. Lower doses of MDMA (e.g., 30 or 75 mg) are expected to have lesser effects on blood pressure and heart rate than 125 mg.

Potential complications of elevated blood pressure or heart rate include stroke or myocardial ischemia. These events have not occurred in clinical trials of MDMA. Excluding people with cerebrovascular or cardiovascular disease will reduce the likelihood of risks arising from the cardiovascular effects of MDMA. Investigators conducting trials of MDMA should be prepared to treat elevated blood pressure with medications if necessary and either to provide appropriate care related to these effects or to transport individuals to an emergency department if necessary.

Because of its activity at $5HT_{2B}$ receptors, it is possible that MDMA could stimulate valvular heart disease (VHD). However, studies in ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential valvular heart disease, and echocardiograms of a small sample of ecstasy users appear normal.

9.2.6. Psychological Risks

Reports of MDMA-assisted psychotherapy conducted prior to the scheduling of MDMA indicate that some people receiving MDMA in a therapeutic context experienced periods of increased anxiety and even panic. Psychological distress from MDMA could arise at any time from the first indications of drug effects until the last effects have dissipated (approximately 3 to 5 hours after drug administration). Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours. In addition, psychological distress could arise following an MDMA session as a result of participants having difficulty integrating their experience after the effects of MDMA have subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from the investigator, with occasional use of benzodiazepines for anxiety more than 24 hours after the experimental session. In clinical trials of PTSD treatment, participants are informed that experimental sessions have the intention of confronting and working through traumatic experiences. Hence signs of psychological distress, anxiety, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. In Phase I trials

with normal volunteers, mild anxiety and depressed mood are reported by some subjects 1 to 3 days after MDMA administration.

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 - 1 or with psychotic disorders)
- preparatory non-drug psychotherapy sessions before the experimental session
- creating an atmosphere of trust during the experimental session
- close monitoring
- daily contact with subjects for the period of a week after the experimental session
- providing non-drug integrative psychotherapy sessions
- having subjects remain at the study site for the night of each experimental session to further reduce psychological distress, and having qualified personnel, such as a trained attendant, available during the overnight stay to respond to the needs of the subject.

Attendants will be instructed to contact the investigator upon request or at the appearance of signs of a potential adverse event. Every effort will be made to help subjects resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the session. Such efforts will include empathic listening on the part of the investigators and affect management techniques such as diaphragmatic breathing by subjects.

At the end of any experimental session, if the subject is still severely agitated or experiencing any other severe psychological distress, the following measures will be taken:

1. If the subject is anxious, agitated, and/or in danger of any self-harm or is suicidal at the end of the MDMA session, the investigators will remain with the subject for at least two more hours. During this time, the investigators will employ affect management techniques reviewed during the introductory sessions and will talk with the subject to help him or her gain cognitive perspective of their experience. If this situation should occur during an integrative therapy session, the same approach will be used, and at least one of the investigators will be available to stay with the subject for at least two additional hours.
2. If a subject remains severely anxious, agitated or in danger of self-harm or suicide, or is otherwise psychologically unstable at the end of this two-hour stabilization period, the clinical investigator will decide between the following options:

    a. A psychiatric nurse, therapeutic assistant, or therapist will stay with the subject until the time of his or her appointment with investigators the next day. The investigators will then meet with the subject daily until the period of destabilization has passed.
    b. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an MDMA session, the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication." Investigators should not prescribe an SSRI, SNRI, MAOI, or any other psychotropic medication in this context. Residual symptoms will be addressed during the frequent follow-

up psychotherapy visits with the investigators.

c. Hospitalization for stabilization. If a subject should become psychotic, arrangements will be made to stabilize and transfer him or her to the study site inpatient unit or the nearest appropriate inpatient psychiatric facility.

Subjects hospitalized after a severe panic reaction will be suspended from further participation in the trial until after recovery or stabilization, at which time the investigator will carefully evaluate the subject's emotional status and decide whether or not the subject may continue the study. For those subjects engaged in an ongoing therapeutic relationship with a psychotherapist or psychiatrist, the subject's outside therapists will be involved in the management of any psychiatric complications.

9.2.7. Risks Related to Body Temperature

Findings from previous Phase 1 trials indicate that MDMA administered in a controlled setting produces only a slight increase in body temperature, and ambient temperature neither increases nor attenuates this slight elevation in humans. Approximately 30% of people with PTSD exhibited an elevation in BT greater than 1 C, but no medical intervention was required in any of these cases. However, hyperthermia has occurred in ecstasy users. Maximum body temperature could rise above normal temperature, as with the maximum peak of 100° Fahrenheit (F), or 37.7 Celsius (C), during the first experimental session in the sponsor's recent Phase 2 trial (n = 23, MDMA and placebo conditions combined). In this study, body temperature returned to normal without treatment other than simply lowering the ambient temperature, which may or may not have been necessary. Investigators should assess body temperature periodically. Sponsor-supported studies have assessed it every 60 to 90 minutes. The investigators must be able to cool body temperature if necessary through removing blankets and layers of clothing, decreasing the ambient temperature and, if necessary, directing a fan toward the subject. Further cooling with ice packs or, if available, a cooling blanket, can be used if these steps do not reduce body temperature. Subjects with signs or symptoms of heat stroke will be transferred to the nearest hospital for treatment.

9.2.8. Immunological Risks

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 and 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 data from the study of MDMA-assisted psychotherapy has reported only instances of infection (upper respiratory) within seven days of MDMA administration. 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.

9.2.9. Reproductive and Developmental Risks

Risks posed to pregnant women by MDMA are not known. One of two studies of ecstasy users suggests 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, and a third study detected a link between degree of self-reported prenatal exposure to ecstasy and delays in infant development. All sponsor-supported trials of MDMA exclude pregnant and lactating women, and women 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 participant becomes pregnant during study participation, the sponsor and clinical investigator will follow the pregnancy to outcome.

9.2.10. Risk of Abuse

Despite its classification as a Schedule 1 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. In two studies of MDMA-assisted psychotherapy for people with PTSD, only one of 32 participants reported using ecstasy subsequent to study participation, and several subjects 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 will be permitted. MDMA will be handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

10. Conclusion

Based on the current state of scientific knowledge, the risk for subjects meeting inclusion and exclusion criteria who are exposed to MDMA at doses used in sponsor-supported studies in a clinical setting appear to be manageable. Future studies conducted by the Sponsor are intended to further develop the safety profile of MDMA in the PTSD subject population. MDMA-assisted psychotherapy appears to be a promising treatment method for chronic PTSD, and more clinical trials in larger subject populations are warranted.

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