INVESTIGATOR'S BROCHURE

SPONSOR: Multidisciplinary Association for Psychedelic Studies

PRODUCT: 3,4-methylenedioxymethamphetamine (MDMA)

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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 that supports research into the therapeutic potential of hallucinogenic compounds and cannabis. MAPS is working to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with posttraumatic stress disorder (PTSD).

This document is the sixth edition of MAPS' Investigator's Brochure (IB) for MDMA. It 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.

4 Introduction

MDMA is not a novel compound, and the history of its use in humans predates nonclinical studies. MDMA was first synthesized and patented by the pharmaceutical company Merck in 1912 [1], but is currently not covered by a patent. The Sponsor holds the Drug Master File with the U.S. Food and Drug Administration (FDA). After MDMA was rediscovered by the chemist Alexander Shulgin [2], he and his colleagues provided initial reports of its pharmacology and effects in humans [3, 4]. MDMA was found to robustly influence human emotional status in a unique way [4] without notably effecting physiological functions, such as visual perception or cognition [5, 6, 7:Vollenweider, 1998 #880].

Shulgin and Nichols were the first to report on the effects MDMA in humans [4]. Shulgin introduced MDMA to a psychotherapist he knew, and the psychotherapist went on to introduce MDMA as a psychotherapeutic adjunct to others, with MDMA-assisted psychotherapy first occurring during the mid to late 1970s. Psychotherapists used it to treat anxiety, depression, and posttraumatic stress disorder [8, 9]. During the early 1980s, increasing numbers of people began using MDMA, sold as "Ecstasy" outside of therapeutic contexts [10]. The first wave of non-medical use occurred not only in dance clubs but also in small groups of people, in a self-exploratory or spiritual context or while attending concerts. Non-medical use continues today in the same contexts [11, 12].

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 [13, 14]. This classification hampered research into the medical uses of MDMA. Prior to this event, MDMA was used by therapists as an adjunct to psychotherapy, although no formal controlled clinical trials to establish safety and efficacy were conducted at the time [15, 16]. Reported effects of MDMA and related compounds include enhanced feelings of closeness to others, empathy, wellbeing and insightfulness [15, 17, 18]. MDMA was used in individual, couple and group therapy to treat diverse psychological disorders, including moderate depression and anxiety [15, 19]. It was also found to be useful in reducing physical pain secondary to certain kinds of cancer [8]. However, shortly after it was scheduled, animal studies described long term decreases in markers of serotonergic functioning after high or repeated doses of MDMA administration [20]. Reports of adverse events seen following MDMA use [21-23] and cognitive, physiological and imaging findings in humans

raised concerns on the safety of MDMA administration [24-28].

To date, MDMA has been administered to over 494 individuals for research purposes without the occurrence of drug-related Serious Adverse Events (SAEs) [29-43]. Placebo-controlled Phase 1 clinical trials have confirmed that MDMA produces an easily controlled intoxication characterized by euphoria, increased well being, sociability, self-confidence, and extroversion, increased anxiety and minor alterations in perception [5-7, 44-47]. Investigators working with the Sponsor have enrolled and treated 47 subjects in Phase 2 clinical trials of MDMA administered in combination with psychotherapy for PTSD patients, with 9 of these subjects treated in 2009. In the same year, 94 subjects participated in research studies not supported by the Sponsor. Studies in healthy volunteers have investigated the acute and sub-acute subjective, psychological, physiological and neuroendocrine effects of MDMA. Initial studies in the 1990s examined the physiological effects of MDMA from a safety perspective, and recent studies have examined the effects of this compound on attention, prosocial effects, memory and brain activity and human drug discrimination.

Based on the current state of scientific knowledge, the safety profile appears favorable for subjects who are exposed to the highest dose of MDMA used in MAPS clinical trial protocols on three separate occasions about a month apart. Knowledge of the mechanism of action of MDMA is far from complete. In order to thoroughly investigate the safety and efficacy of MDMA-assisted psychotherapy as an evidence-based treatment for PTSD, more clinical trials are warranted.

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 methylhydrastinin as a phenylisopropylamine derivative of safrole, an aromatic oil found in sassafras, nutmeg, and other plants [48].

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [48, 49]. 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 [50, 51] and self-administration in primates [52] suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. It seems that R(-)-MDMA may have hallucinogen-like effects, compared to S(+)-MDMA, which exhibits psychomotor stimulant-like effects. According to an *in vivo* microdialysis study, S(+)-MDMA may be associated with greater dopamine release in specific brain areas [53]. 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 [54]. MDMA available for human use is racemic, containing roughly equal amounts of both enantiomers. Any differential effects of the enantiomers remain untested in humans.

For clinical trials, the Sponsor has made arrangements to use 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 [55]. 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. Full dose is 125mg, 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).

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 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. While MDMA also has some affinity for specific serotonin, norepinephrine, acetylcholine and histamine receptors, strength of activity on these receptors is low in comparison to monoamine transporters [56-59]. Recent *in vitro* studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptake [60, 61] and that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine [62]. 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 [63-65]. 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 [66-68].

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 [69]. 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 [70]. Recent reports re-examining these effects have questioned the applicability of interspecies scaling models for MDMA and supported nonlinear pharmacology [71-73]. 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 [74, 75]. 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 [71]. 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 [76, 77]. 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 [78]. 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 [79, 80], and some drug discrimination studies suggest that the $5HT_{1A}$ agonist 8-OH-DPAT partially or fully substitutes for MDMA [81-83]. 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 [84, 85]. 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 [86].

6.2.2 Gene Transcription in Animals

A number of research teams have studied the effects of MDMA on gene expression in rodents. 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 transcripts for genes that regulate the GABA transporter [87, 88]. Some of the increased gene transcripts are associated with monoamine release [87]. Investigations with serotonin transporter knockout mice suggest that at least some of these changes in gene transcription are related to serotonin release. 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 [89]. Increases in transcripts of genes regulating extracellular signaling in mice were also reported [90]. It appears that serotonin may play more of a significant role than dopamine in transcription-level changes [89]. 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 [91-93], 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 [94]. 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 [54].

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 [95]. Moderate and high doses of MDMA elevate body temperature and disrupt thermoregulation in rodents [64], and doses of MDMA in the 1 to 2 mg/kg range only cause a slight increase in body temperature [96]. 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 [97-99]. High doses of MDMA also produce significant elevations in body temperature in primates [72, 100, 101]. At doses closer to those humans ingest [30], monkeys exhibit only slight to moderate elevation in body temperature [102, 103]. 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 [30, 102, 103], though at least one study in monkeys found that ambient temperature modified the effects of 1.5 mg/kg i.v. in monkeys [104]. 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 [64]. Injections of 20 mg/kg MDMA in conscious rodents assessed by radiotelemetry found that MDMA caused a prolonged increase in blood pressure [105]. 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 [105]. The researchers found that MDMA has both pressor and depressor effects, acting through adrenergic receptors [105-107]. A study in rodents suggests that norepinephrine may play a role in cardiovascular effects [108]. 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 [64, 109]. Rats given lower doses of MDMA exhibited increased anxiety in the elevated plus maze [110], 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 [109]. 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 [64]. However, it is notable that a recent publication failed to find thigmotaxis in rats given 5 mg/kg MDMA [111]. In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA [103].

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 [84]. 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 $5HT_{1A}$ receptor agonism, with the oxytocin increase arising from the indirect effects of MDMA on $5HT_{1A}$ receptors [85, 112]. To date, there have been no human pharmacological challenge studies combining MDMA with $5HT_{1A}$ agonists or antagonists, and only a pair of reports from the same challenge study with a $5HT_{1A}$ antagonist [31, 113]. 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 [114-117].

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 [64, 109, 118-120]. Studies in rodents and primates suggest that MDMA could damage serotonin axons and cause neurotoxicity [64, 121-124]. However, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses. It now appears that lower doses of MDMA do not reduce brain serotonin [72, 73]. 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 [125]. Rats receiving lower doses of MDMA also fail to exhibit signs of neurotoxicity [73]. 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 [126].

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 [69]. Interestingly, the LD50 in mice housed together is 20 mg/kg, considerably lower than values in isolated animals [98, 127].

6.3.3 Developmental Toxicity in Animals

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 [128]. 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 [129]. 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 [130] and that a region-specific enhancement in BDNF expression did not mediate the abnormal serotonergic signaling observed following neonatal MDMA exposure [131]. Postnatal days 11 and 20 were proposed to be equivalent to the third trimester of gestation in humans [129], 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 [128]. 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 [130]. 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 headweaving stereotypy [132]. Another team also found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA [133]. 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 [134-136]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [134], 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 [137, 138]. 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 [2], and there are records of a police seizure of MDMA in the early 1970s [139]. Shulgin and Nichols were the first

to report on the effects of MDMA in humans [4]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat anxiety, depression, and PTSD [15]. Legal therapeutic use continued until its placement in US Schedule 1 in 1985 [8, 17, 140]. Estimates indicate that 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling [2, 140]. A few uncontrolled human studies of MDMA occurred in the 1980s [141, 142], 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 [143]. The Sponsor has completed an investigation on the use of MDMA-assisted psychotherapy for PTSD under the U.S. IND #63,384 in the U.S., and a second study is collecting follow-up data in Switzerland [144, 145]. The Sponsor is currently planning future clinical trials based on the results of these two pilot studies.

7.1 Pharmacology and Product Metabolism in Humans

7.1.1 Pharmacology in Humans

Many researchers categorize MDMA as belonging to a unique class of drugs referred to as the entactogens [18, 117]. Entactogens are reported to 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 [5, 7, 44, 146], but it also appears to share qualities with a small number of pharmacologically related compounds, such as methylenedioxyethylamphetamine (MDE) [146]. Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecstasy [114-116, 147]. To date only two controlled studies have sought to measure these effects [6, 45]. Although researchers have offered several models and explanations for the effects of entactogens, it appears that release of serotonin plays a significant role in producing at least some of these effects. Indirect action on $5HT_{1A}$ or $5HT_{2A}$ receptors and neuroendocrine responses such as increases in the hormones oxytocin, vasopressin, prolactin, and cortisol may also play a role in producing the unique effects of MDMA.

Estimates from animal data suggest the LD50 in humans is probably between 10 - 20 mg/kg [48]. Typically, human trials have used doses between 1 and 2 mg/kg, with the design of the 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. Human MDMA studies suggest that serotonin release plays a prominent role in producing the 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 [45, 148-151]. 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 [148]. Some researchers report that SSRIs attenuate MDMA-induced increases in heart rate and blood pressure [45, 149] while others report that SSRIs only attenuate elevated heart rate [151]. 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 [152].

In contrast, the $5HT_{1A}$ receptor appears to be minimally involved in producing the subjective effects of MDMA. Co-administration of the beta-blocker and $5HT_{1A}$ antagonist pindolol along with 1.5 mg/kg MDMA to 15 men only attenuated self-reported "dreaminess" and pleasantly experienced derealization after MDMA, without actually attenuating MDMA-related reduction in performance on a task requiring visual attention [31].

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 [153]. There are no reports examining the contribution of norepinephrine release to MDMA effects in humans.

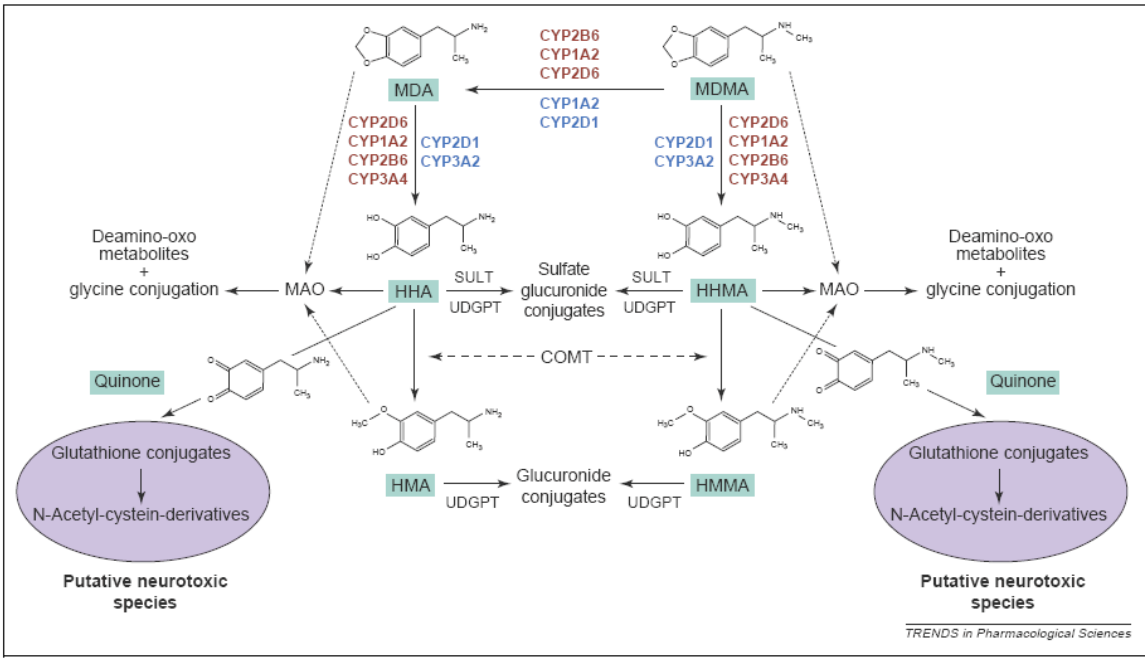

Figure 1. Metabolism of MDMA in humans (in red) compared to metabolism in rats (in blue). Reproduced with permission of R. de la Torre [154].

7.1.2 Metabolism in Humans

Metabolites of MDMA are summarized in Figure 1 [155-159]. Metabolites are primarily excreted as glucuronide and sulfate conjugates [156]. Studies examining metabolism of 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates [160-164]. Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 mol and 17.7% recovery [164]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [165]. 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 [160]. 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 [166], suggesting that secondary metabolism of MDMA continues during this period.

Onset of MDMA effects occurs 30 to 60 minutes after administration [5, 167], peak effects appear 75 to 120 minutes post-drug [7, 33, 44], and duration of effects lasts from three to six hours [6, 44, 117], with most effects returning to baseline or near-baseline levels six hours after drug administration. Orally administered MDMA has a half-life of seven to nine hours in humans. 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 [168]. The enzyme COMT and monoamine oxidase may also be involved in the metabolism of MDMA [165].

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 [6, 143, 160, 167, 169], whereas growth hormone is unchanged by up to 125 mg MDMA [167]. Increases in cortisol and prolactin peak at about 2 hours after MDMA administration. 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 [170], and a dose of 100 mg MDMA given 24 hours after an initial dose stimulates a greater release of cortisol but not prolactin [160]. A naturalistic study in clubgoers found a much greater elevation in cortisol after ecstasy use [171]. 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 [6]. MDMA produces a robust increase in the neurohormone oxytocin [172], a finding first seen in a naturalistic study [173]. The naturalistic study reported elevated levels of the hormone oxytocin in clubgoers with detectable blood MDMA levels when compared with 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 [174-177].

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 [143]. 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 [44, 149, 152] and this elevation was unaffected by ambient temperature [30]. 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 [30]. The same study found that ambient temperatures did not affect elevation in core temperature after administration of MDMA, which increased metabolic rate. 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. Men seem to exhibit a greater elevation in body temperature than women when given the dose of MDMA in milligrams per kilogram [44]. 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 [171, 178, 179].

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 [180, 181]. 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 [182]. A case report and some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans [183, 184]. 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 [141] and replicated by other research teams in the US and Europe [44, 167, 185]. Elevation in blood pressure above 140/110 or higher occurred in approximately 5% of research participants receiving at least 100 mg MDMA in research studies [117, 167], but none of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [117, 167]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [6]. 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 [141] and peak between 1 and 2 hours post-drug [7, 185], 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 they also exhibited a greater elevation in heart rate than women, as reported in a study summarizing and pooling data from a series of human MDMA studies [44]. These studies did not report any discomfort or increased distress accompanying cardiovascular effects.

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 [186-188], such as stroke, cardiac events or other cerebrovascular events, including cerebral venous sinus thrombosis [189] and cerebral hemorrhage, [21, 190-192]. In two such cases a previously existing underlying arteriovenous malformation appeared to play a role in the event [190, 192]. Increased heart rate (tachycardia) and elevated blood pressure can also lead to cardiac events, such as arrhythmias or myocardial infarction [193, 194]. 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 [57]. Studies in ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential valvular heart disease [195]. 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 [185].

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, making it the third most common serious adverse event in reported in the literature [70]. There appears to be more than one pattern of ecstasy-related hepatotoxicity. Acute liver failure or hepatitis has occurred after reported ingestion of a single ecstasy tablet [196-198]. In other cases, hepatotoxicity has occurred after months of regular ecstasy use [199]. Standard toxicity studies failed to find liver damage after MDMA in rats or dogs after 28 days of exposure [200], 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 [201], increase profibrogenic activity in cultured stellate cells [202] and slightly reduce cell viability without producing lipid peroxidation [203]. 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 [150, 170, 204, 205]. 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 [205, 206]. 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 [170, 207], and 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 [170]. 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.

7.2.6 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 [43] 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 [43]. 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 [43]. Another study found no differences in baseline sleep using electroencephalography (EEG) [208]. In this study, acute depletion of tryptophan, the precursor for serotonin, increased REM sleep and the amount of stage 2 sleep in both samples, and the samples did not differ in baseline mood.

Early studies reported significant decreases in total sleep as well as stage 2 sleep in regular ecstasy users [209], 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[210, 211]. However, the differences between the groups were subtle and only evident in the context of disrupting catecholamine synthesis. Both studies consisted largely of samples of heavy ecstasy users, and one study detected an association between degree of ecstasy use and effects on sleep [210]. Taken together, correlations suggested by McCann and colleagues in heavy ecstasy users do not seem to be replicated by prospective studies.

A study of breathing during sleep in 71 ecstasy users and 62 polydrug users did not find overall differences in disrupted breathing as assessed via nasal cannula, but found that all moderate and severe breathing disruptions occurred in the ecstasy using sample [212]. 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, the two studies of sleep EEG did not find greater numbers of nighttime awakenings or disrupted sleep such as would be expected to be present if these subjects actually had sleep apnea [43, 208]. Furthermore, McCann and colleagues' surprisingly high overall detection rate of disrupted breathing (27%) in the control group of healthy, non-obese participants raises questions about the significance of this measure as an indicator of sleep apnea. Finally, mean ecstasy use in all studies was greater than five times and the required minimal lifetime usage was greater than 25 in the studies of McCann and colleagues, and so the results of these studies may be may not be applicable to estimations of the risk of three administrations of MDMA to participants in MAPS clinical trials.

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7.2.7 Effect on Homeostasis in Humans

A number of case reports describe hyponatremia after uncontrolled, non-medical ecstasy use [70, 180, 213, 214]. 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. Hyponatremia has not occurred during a controlled clinical trial with MDMA.

7.2.8 Reproductive and Developmental Risks in Humans

Previous research supported a possible link between ecstasy use and birth defects [215], 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 [216]. 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 [217]. As of early 2010, there have been no further investigations into the developmental effects of ecstasy use in humans.

7.2.9 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 [218], though other reports of non-representative samples have reported higher percentages of MDMA abuse or dependence [219], and approximately 25% of polydrug users who had used ecstasy reported abuse or dependency [220]. 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, [44]. 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.

7.3 Neuropsychological Effects in Humans

7.3.1 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 [29, 44]. Effects peak 90 to 120 minutes after oral administration and they are near to or at pre-drug levels three to six hours later [47, 117, 221]. Sub-acute effects may occur one to three days after drug administration, but are no longer apparent seven to 14 days later [6, 222, 223]. 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 [142, 144, 224]. Though a naturalistic study reported that ecstasy increased accuracy of assessing at

least some emotional expressions [225], a controlled study with 0.75 and 1.5 mg/kg MDMA failed to replicate this finding [226].

7.3.2 Emotional Effects in Humans

MDMA increases positive mood and anxiety [5-7, 44]. MDMA users report feeling more talkative and friendly after receiving MDMA, and at least one research team informally reported increased feelings of closeness to others [117]. 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 [6], 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 [45]. People reported feeling anxious and undergoing negatively experienced derealization, including increased anxiety related to loss of control and experiences of racing or blocked thoughts [5, 44, 117].

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 [5-7, 44]. More surprisingly, participants report increased positive mood even after a dose of 25 mg [227]. 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, 153].

Positron emission tomography (PET) brain scans 75 minutes after administration of 1.7 mg/kg MDMA found increased regional cerebral blood flow (rCBF) in prefrontal, inferior temporal, and cerebellar areas and decreased rCBF in the left amygdala [228]. Decreased activity in the amygdala may be indicative of reduced reactions to potential threats [229]. 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 [226]. 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.

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 [114-116, 230]. 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, and are the most common reason for appearance at an emergency department [70]. 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 [231]. 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 [232] 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 [181, 233]. 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.

7.3.3 Perceptual Effects 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 [5, 44]. Participants also experienced altered time perception and changed meaning or significance of perceptions after MDMA [117]. 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 [6, 7]. Women reported experiencing all subjective effects of MDMA more intensely, but especially those related to perceptual changes [44]. 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 [152], while coadministration with the 5HT1A antagonist pindolol did not [31].

7.3.4 Cognitive Effects in Humans

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 [35, 36, 234]. 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 [40]. MDMA acutely improved performance on one measure of impulsivity while failing to affect performance on other impulsivity measures [234]. 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 [35, 36, 40]. These changes in cognitive function and psychomotor skills occurred during peak drug effects but were not detectable 24 hours later.

7.3.5 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 [41]. 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 [235]. However, a comparison between heavy ecstasy users and non-user controls failed to find differences in baseline rCBF [228], and a report assessing changes before and after initial use found increased rCBF in only one area of the prefrontal cortex [236], 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 [237]. 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.

7.3.6 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 [24-26, 238]. These early investigations possessed a number of methodological flaws, including retrospective design and poor matching of ecstasy users with appropriate controls [70, 239, 240]. 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 [241-244]. Some of these investigators also conducted longitudinal studies, comparing ecstasy users, sometimes alongside controls, at two separate time points [245-247]. For the most part, these 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. One study has failed to detect differences in SERT sites between ecstasy users and polydrug user controls, using the same radiolabeled compound as used by McCann and colleagues in their recent study [248], and another found modest reductions in estimated SERT sites in ecstasy users versus non-drug using or cannabis-using controls [249]. Studies in very moderate ecstasy users failed to see an increase in this marker [236], and only one of three studies of this marker in humans detected it in heavy users [250-252]. 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 [236, 253].

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 [254]. Two independent meta-analyses of memory in ecstasy users arrived at somewhat contradictory conclusions [255, 256]. While both analyses detected an association between ecstasy use and impaired performance on at least some measures of memory, the analysis by Laws and Kokkalis found that this association had a medium to large effect size with no effect of ecstasy dose, while Zakzanis and colleagues reported that the association had a small to medium effect size with an ecstasy dose effect. Zakzanis and colleagues also concluded that polydrug use independently impaired cognitive function. Minimum cumulative use in both analyses was above 10 uses, and average cumulative use was considerably higher (287

tablets in Zakzanis' analysis and 327 in Laws and Kokkalis' paper). Schilt and colleagues performed a prospective study of cognitive function in people before and after reporting ecstasy use. In this study, comparing 58 people reporting use of 3.2 tablets with 60 controls before and after use, up to 18 months later, and found an association between ecstasy use and performance on measures of verbal memory, and not attention or working memory [257]. While all participants exhibited scores within the normal range at both times they were tested, people who did not use ecstasy showed greater improvement in performance than did people who used it. Analyses in the study assessing cognitive function apparently included one individual reporting use of 30 tablets. Another prospective study conducted by the same team examined working memory in 25 people reporting an average use of 2 tablets with 24 controls, failing to find any significant differences either in brain activity as assessed via functional magnetic imagery (fMRI) or on working memory and selective attention [258].

Previous research has established a link between repeated ecstasy use and impaired executive function, defined as planning, decision-making, and inhibiting well-learned responses [259]. 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, particularly heavy users [243, 260], and others failing to find differences between ecstasy user and non-user executive function [244], or finding executive function impairments only in male ecstasy users [261]. Current studies continue to support both presence and absence of a relationship between ecstasy use and executive function. It is also possible that polydrug use may contribute to ecstasy users' impaired executive function [262, 263].

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 [264-266], though other studies continue to find consistent differences, particularly in verbal memory [211, 249, 267]. Several reports have found relationships between cognitive function and use of other drugs [264]. Taken together, there continues to be consistent evidence of small but detectable impairments in specific areas of cognitive function in moderate to heavy ecstasy users, with these findings likely to be influenced by multiple factors. No impaired cognitive function was found in subjects who received two doses of MDMA in a therapeutic context when compared with participants receiving placebo [144].

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 [25, 268]. Recent studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions [266, 269, 270]. Two recent studies even used the same measure of behavioral impulsivity in samples of heavy ecstasy users yet obtained different findings [266, 269]. 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 [223, 271, 272]. The relationship between drug use, including ecstasy use, and impulsivity, is complex. Taken together, self-reported changes or deterioration in psychological well-being and impulsivity in ecstasy users are likely multiply determined and only partially, if at all, uniquely related to ecstasy use.

Previous reports have found an association between ecstasy use and increases in symptoms of depression or anxiety, (see for example [273, 274]). 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 [275]. Investigators noted that the association was strongest in studies with small samples, and noted that drug use variables are often incompletely reported and not verified through any methods save self-report in these studies. Findings concerning the long-term effects of ecstasy use on mood, including findings from longitudinal studies, suggested that an association between increased feelings or symptoms of anxiety and depression and ecstasy use exists, but that these findings were more strongly related to polydrug use rather than to use of any one substance [262, 276, 277].

7.4 Adverse Events and Side Effects 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 [10, 11, 116, 259, 278]. 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 [279, 280]. These include hyperthermia, psychiatric problems, hepatotoxicity and hyponatremia. 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 [180]. Hall and Henry address medical emergencies related to ecstasy use [281]. 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 [181, 233, 282]. 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 [254]. As is the case with fatalities, medical emergencies after ecstasy use are more likely to occur in men [181].

Other serious adverse events occurring after ecstasy use include cardiac problems (as arrhythmias), cerebrovascular events, hematological, respiratory events (as pneumomediastinum)), dermatological, ophthalmological and dental events, as described in previous editions of the Investigators Brochure [70].

7.4.1 Common Adverse Events Reported after MDMA

Common adverse and side effects of MDMA include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils [6, 44, 167, 283]. Some reports indicated decreased rather than increased alertness [5]. Other common side effects 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 [117], and unusual thoughts or ideas [6]. Other less common side effects include parasthesias (unusual body sensations) such as tingling or feeling hot or cold. 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 side effects of MDMA, though men were more likely than women to experience the specific side effects of nausea and sweating [44]. Side 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 [224].

Table 1: Acute Side Effects of MDMA Compiled from Literature of Human Trials with MDMA [70].

Data Source	**Prevalence** Across Literature		Downing 1986	Gamma et al. 2000	Greer & Tolbert 1986	Liechti, Saur, et al. 2000	Liechti & Vollenweider 2000a	Liechti & Vollenweider 2000b	Vollenweider et al. 1998
	Placebo	**MDMA**							
N:	**13-57**	**13-112**	**10**	**16**	**29**	**14**	**14**	**16**	**13**
MDMA Dose(s):	0	0.5-4.18 mg/kg	1.76-4.18 mg/kg	1.7 mg/kg	75-150, 200 mg	1.5 mg/kg	1.5 mg/kg	1.5 mg/kg	1.7 mg/kg
Time post-drug	-	-	2-5 hr	N/A	N/A	N/A	N/A	N/A	0-3 hr
Lack Of Appetite	2%	70%	100%	63%	97%	50%	50%	50%	62%
Jaw Clenching	0%	63%	60%	64%	76%	57%	71%	44%	62%
Dry Mouth	N/A	57%	N/A	N/A	N/A	57%	57%	N/A	N/A
Thirst	4%	48%	N/A	50%	N/A	57%	57%	38%	38%
Restless Legs	0%	45%	N/A	N/A	N/A	N/A	N/A	44%	46%
Impaired Balance/ Gait	0%	44%	70%	N/A	10%	71%	43%	50%	62%
Concentration issues	16%	42%	30%	50%	3%	71%	50%	63%	62%
Dizziness	2%	40%	N/A	N/A	N/A	57%	21%	50%	31%
Restlessness	0%	39%	N/A	N/A	N/A	50%	29%	44%	31%
Sensitivity To Cold	7%	38%	N/A	N/A	N/A	N/A	N/A	N/A	38%
Private Worries	23%	38%	N/A	N/A	N/A	N/A	N/A	N/A	38%
Heavy Legs	0%	38%	N/A	N/A	N/A	N/A	N/A	N/A	38%
Palpitations	0%	33%	N/A	38%	N/A	43%	21%	N/A	31%
Feeling Cold	4%	33%	N/A	N/A	N/A	43%	N/A	N/A	23%
Perspiration	0%	30%	N/A	50%	N/A	36%	N/A	N/A	0%
Drowsiness	50%	23%	N/A	N/A	14%	43%	N/A	N/A	N/A
Nystagmus	N/A	23%	80%	N/A	3%	N/A	N/A	N/A	N/A
Hot Flashes	0%	23%	N/A	N/A	N/A	N/A	N/A	N/A	23%
Nausea	4%	21%	10%	N/A	24%	36%	N/A	N/A	8%
Trismus	N/A	21%	N/A	N/A	3%	57%	N/A	N/A	N/A
Inner Tension	0%	17%	N/A	N/A	3%	43%	14%	19%	23%
Insomnia	0%	17%	0%	N/A	N/A	N/A	N/A	N/A	31%
Anxiety	0%	16%	N/A	N/A	17%	14%	N/A	N/A	N/A
Weakness	0%	16%	N/A	N/A	3%	36%	N/A	N/A	23%
Urge To Urinate	8%	15%	N/A	N/A	N/A	N/A	N/A	N/A	15%
Tremor	0%	14%	N/A	N/A	3%	21%	14%	N/A	31%
Muscle Ache/ Tension	N/A	14%	N/A	N/A	21%	N/A	N/A	N/A	0%
Forgetfulness	0%	14%	N/A	N/A	3%	N/A	N/A	N/A	38%
Fatigue	26%	13%	N/A	N/A	7%	N/A	29%	N/A	8%
Parasthesias	0%	12%	N/A	N/A	3%	N/A	N/A	N/A	31%
Lack Of Energy	14%	12%	N/A	N/A	3%	29%	N/A	N/A	N/A
Brooding	0%	12%	N/A	N/A	3%	29%	N/A	N/A	N/A
Fainting	N/A	3%	N/A	N/A	3%	N/A	N/A	N/A	N/A
Blurred Vision	N/A	3%	N/A	N/A	3%	N/A	N/A	N/A	N/A
Lip Swelling	N/A	2%	N/A	N/A	3%	N/A	N/A	N/A	0%
Headaches	N/A	2%	0%	N/A	3%	N/A	0%	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 [284, 285]. The first double blind, placebo controlled U.S. Phase 1 study sanctioned by the FDA and supported by the Sponsor was conducted in 1994 [143]. 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 [224]. This placebo controlled, double blind dose response study was the first Phase 2 study funded by the Sponsor. A local Ethics Committee and the Spanish Ministry of Health originally approved the protocol 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 population appeared promising as neither 50 nor 75 mg MDMA were found to increase psychopathological symptoms in this patient population. The Sponsor has recently 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, referred to hereafter as MP-1 [144]. Analysis of the results from this small pilot study from 20 subjects randomized to 125mg MDMA (N=12) 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 [144]. The Sponsor supports a second study in Switzerland, referred to as 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. Currently, one participant remains to complete the follow-up assessment a year after receiving MDMA. Results from this study will be added to future editions of the IB upon publication.

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 who was a male veteran that refused prior treatment, was also enrolled after approval of an amendment by the FDA. Eighteen of the participants were women and five were men, and all were European American. All participants were at least 18 years old, between the ages of 26 and 56 (average age = 40.6 years). There were no differences in age across the two conditions $F(1, 21) = 0.0$. Enrolled subjects had no history of major medical conditions, psychotic disorders, dissociative identity disorder or personality disorders. Safety data obtained from this study includes: scores from tests of cognitive function performed before and after study participation, vital signs and a measure of psychological distress during experimental sessions, expected side effects for three experimental sessions, and adverse events that occurred during the study.

One female and one male subject withdrew from the study after the first experimental session. The male subject withdrew from the study due to financial constraints on travel reimbursements. The female subject experienced benzodiazepine withdrawal while tapering off medication after enrollment, but prior to drug administration. This event led to hospitalization. The same subject experienced a relapse in depression occurring 42 days after MDMA administration. This relapse required medication and led to withdrawal from the study. 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.

8.1.1 Vital signs

As expected, vital signs during the first experimental session indicate that MDMA elevated blood pressure and heart rate, but that elevations returned to baseline or near-baseline seven to eight hours after drug administration.When analyzed with one-way analysis of variande (ANOVA), peak elevation in systolic blood pressure and heart rate during the first experimental session reached statistical significance. Elevation in diastolic blood pressure and body temperature, while detectable, did not reach significance. The same results occurred for the second experimental session. The addition of a supplemental dose of MDMA did not increase peak values for any of the vital signs measured during the experimental session.

Table 2a: Peak Values of Vital Signs During Experimental Session 1

Condition	Peak SBP		Peak DBP		Peak Temp		Peak Pulse	
	M	SD	M	SD	M	SD	M	SD
Placebo (n=8)	127.7	16.9	83.8	11.7	98.3	0.6	82.8	7.7
MDMA (n=15)	147.3	19.9	89.7	10.1	98.5	0.7	101.3	17.5

Table 2b: Peak Values for Vital Signs for Experimental Session 2

Condition	Peak SBP		Peak DBP		Peak Temp		Peak Pulse	
	M	SD	M	SD	M	SD	M	SD
Placebo (N = 8)	127.6	14.6	85.4	9.6	98.5	0.67	82.3	11.7
MDMA (N = 13)*	147.8	18.5	90.0	10.1	98.7	0.63	102.4	16.9

*Two participants assigned to the MDMA condition withdrew after the first experimental session but prior to the second experimental session

Table 2c: Peak Values of Vital Signs During Experimental Session 1: Average Values With and Without a Supplemental Dose

Condition	Peak SBP		Peak DBP		Peak Temp		Peak Pulse	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Placebo/no supplement (N = 4)	124.8	22.2	82.00	15.25	98.40	0.75	82.50	9.10
Placebo/ supplement (N = 4)	130.8	12.5	85.5	8.8	98.3	0.6	83.0	7.4
MDMA/no supplement (N = 9)	141.7	17.5	86.2	9.83	98.7	0.6	102.6	18.9
MDMA/ supplement (N = 5)	155.8	22.0	95	8.8	98.5	0.7	99.5	16.6

Table 2d: Peak Values For Vital Signs For Experimental Session 2: Average Values With and Without A Supplemental Dose

Condition	Peak SBP		Peak DBP		Peak Temp		Peak Pulse	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Placebo/no supplement (N = 3)	134.67	23.60	88.67	13.50	98.63	0.60	79.00	5.57
Placebo/ supplement (N = 5)	123.40	6.02	83.40	7.57	98.40	0.78	84.2	14.60
MDMA/no supplement (N = 5)	153.20	21.30	92.0	12.25	98.90	0.63	111.40	16.32
MDMA/ supplement (N = 8)	144.38	17.17	88.75	9.16	98.59	0.65	96.75	15.67

8.1.2 Psychological Effects

Psychological distress of participants was assessed periodically throughout experimental sessions with the single-item, seven-point Subjective Units of Distress (SUD). One-way analyses of variance comparing peak SUD scores in the MDMA and placebo conditions found no difference in peak levels of distress for either the first ($F, (1, 21) = 1.29$, p. > 0.05) or second ($F (1, 19) = 1.25$, $p > 0.05$) experimental session.

Table 3: Subjective Units of Distress During the First and Second Experimental Sessions

Experimental Session #	**Condition**	**Peak SUD score**	
		Mean	SD
Experimental Session 1	Placebo (N = 8)	5.38	1.69
	MDMA (N = 15)	4.47	1.88
Experimental Session 2	Placebo (N = 8)	5.00	1.50
	MDMA (N = 13)	4.15	1.77

8.1.3 Expected Adverse Events

Spontaneously reported expected side effects were collected during the day of each experimental session and for seven days after each session. The investigators derived the list of expected side effects through examination of the literature (see Table 1). Anxiety, headache, tight jaw and fatigue were commonly listed during experimental sessions. While anxiety, headache, fatigue, insomnia and lack of appetite were reported by 40% to 80% of participants in both conditions (see Table 4a), tight jaw, nausea, impaired gait/balance, and feeling cold were more often reported in the MDMA than the placebo condition, and irritability slightly more likely to be reported in the placebo than the MDMA condition. Most side effects reported were mild or moderate, with the majority of effects reported during the experimental session, and fewer effects reported during the seven day interval.

Table 4a: Expected Adverse Events Reported By Participants In MP-1 On Day Of Randomized Or Open Label Experimental Session

	Experimental Session 1		Experimental Session 2		Open Label Session 1 / Naive	Open Label Sessions Mean/ Non-Naïve*
Adverse Event	MDMA (N = 15)	Placebo (N = 8)	MDMA (N = 13)	Placebo (N = 8)	MDMA (N = 7)	MDMA (N = 16)
	% reporting	% reporting	% reporting	% reporting	% reporting	% reporting
Anxiety	60%	62.5%	61.5%	100%	85.7%	56.3%
Headache	53.3%	62.5%	53.9%	50.0%	57.2%	43.8%
Heavy legs	13.3%	0%	0%	0%	0%	0%
Irritable	6.7%	0%	7.7%	37.5%	14.3%	6.3%
Tight jaw	73.0%	12.5%	77.0%	25.0%	85.7%	56.3%
Low mood	13.3%	12.5%	15.4%	12.5%	0%	0%
Nausea	40.0%	25.0%	46.2%	0%	42.9%	25.0%
Parasthesias	20.0%	0%	0%	0%	0%	0%
Restless	6.7%	12.5%	30.8%	12.5%	28.6%	18.8%
Drowsy	13.3%	2.0%	0%	12.5%	14.3%	6.3%
Fatigue	40.0%	50.0%	53.9%	50.0%	28.6%	50.0%
Insomnia	60.0%	75.0%	46.2%	50.0%	28.6%	50.0%
Private Worries	0%	12.5%	7.7%	0%	0%	0%
Thirsty	0%	12.5%	15.4%	0%	42.9%	12.5%
Difficulty concentrating	6.7%	12.5%	23.1%	0%	0%	0%
Impaired gait/balance	26.0%	12.5%	23.1%	0%	14.3%	37.5%
Feeling cold	33.3%	12.5%	46.2%	25.0%	57.2%	56.3%
Perspiration	6.7%	0%	15.4%	12.5%	57.2%	37.5%
Dizzy	40.0%	25.0%	38.5%	0%	42.9%	31.3%
Dry mouth	20.0%	0%	15.4%	0%	57.2%	25.0%
Feeling weak	0%	12.5%	7.7%	0%	0%	6.3%
Loss of appetite	26.7%	12.5%	38.5%	0%	57.2%	75.2%
Nystagmus	13.3%	0%	0%	0%	14.3%	37.5%
Need More sleep	0%	0%	0%	12.5%	0%	0%

*Note pertaining to Table 4a above: Mean percentage for non-naïve open label sessions included: Stage 2 Session 2 (N = 7), Stage 2 Session 3 (N = 4) and Post Stage 1 open-label for MDMA participants (N = 5). Participants in Stage 2 Session 3 were a subset of participants in Stage 2 Sessions 1 and 2.

Table 4b: Expected Adverse Events Reported Within Seven Days Of The First And Second Experimental Sessions In MP-1

Adverse Event	**Seven Days After Experimental Session 1**		**Seven Days After Experimental Session 2**	
	MDMA (N = 15)	Placebo (N = 8)	MDMA (N = 13)	Placebo (N = 8)
	% reporting	% reporting	% reporting	% reporting
Anxiety	66.7%	62.5%	46.2%	75.0%
Headache	20%	25.0%	23.1%	25.0%
Heavy legs	0%	0%	0%	0%
Irritable	26.7%	50.0%	46.2%	37.5%
Tight jaw	26.7%	0%	23.1%	25.0%
Low mood	33.3%	62.5%	46.2%	37.5%
Nausea	33.3%	50.0%	30.8%	0%
Parasthesias	0%	0%	0%	0%
Restless	6.7%	0%	0%	0%
Drowsy	0%	12.5%	0%	12.5%
Fatigue	66.7%	87.5%	76.9%	62.5%
Insomnia	40.0%	62.5%	30.8%	50.0%
Private Worries	13.3%	25.0%	7.7%	0%
Thirsty	0%	0%	0%	0%
Difficulty concentrating	20.0%	25.0%	15.4%	12.5%
Impaired gait/balance	0%	12.5%	0%	0%
Feeling cold	6.7%	0%	0%	0%
Perspiration	0%	12.5%	0%	0%
Dizzy	26.7%	12.5%	7.7%	0%
Dry mouth	6.7%	0%	0%	0%
Feeling weak	26.7%	0%	7.7%	0%
Loss of appetite	33.3%	0%	30.8%	0%
Nystagmus	0%	0%	0%	0%
Need More sleep	20.0%	12.5%	15.4%	12.5%

8.1.4 Unexpected Adverse Events

One hundred twenty three adverse events were reported as occurring during this study. The majority of the adverse events (52/123) were deemed possibly related to the study drug, with relationship assignment made while the investigator was still blinded if they occurred during the randomized study segment of the study. Two frequently reported adverse events occurring during experimental sessions distinguished between participants receiving MDMA and placebo. Participants receiving placebo were more likely to report experiencing pain than participants receiving MDMA, and somatic sensations (as well as the expected side effect parasthesias) were more likely to be reported by people in the MDMA condition. Diarrhea was listed four times (3.3% of all AEs) and only in people after receiving MDMA, albeit not always on the day of the experimental session. It was twice listed by one participant and once by three other participants after receiving MDMA, either as part of the randomized study segment or during an open-label session. Exacerbated body pain (face, knee, thigh, chest, etc.) was mentioned seven times by four subjects, but only participants who received placebo reported this event. Three mentions of stomach or epigastric burning (two in one subject) occurred after MDMA. Single instances of events included vomiting (after MDMA), dysuria (after MDMA), nocturia (sleep interrupted by need to urinate) (after MDMA), myoclonic jerks (after MDMA), dry, itchy skin (after placebo), and visual alterations, as increased visual contrast (after MDMA) that lasted up to five days rather than resolving sooner. The investigator deemed six instances of upper respiratory or other (urinary) infections as "possibly related" to the study drug as a result of previous studies demonstrating transient immunosuppresion.

Table 5a: Unexpected Adverse Events Deemed Possibly Or Probably Related Occurring During And Seven Days After Drug Administration By Condition.

Notation in parentheses: number of participants reporting an event. A single individual can report an event more than once (such as once after each of two experimental sessions).

Adverse Event	**Placebo**	**MDMA**	**Open Label**
	x/16 (N = 8)	x/28 (N = 15)*	x/23 (N = 12)†
Agitation	0	0	4% (1)
Anxiety	19% (2)	0	4% (1)
Anxiety Aggravated	0	0	13% (2)
Appetite absent	0	4% (1)	0
Back muscle spasms	6% (1)	4% (1)	0
Back pain	0	4% (1)	0
Blistering of mouth	0	4% (1)	0
Blurred vision	0	4% (1)	0
Burning finger	0	4% (1)	0
Burning leg	6% (1)	0	4% (1)
Concentration ability impaired	0	4% (1)	0
Derealization	0	4% (1)	0
Detachment	0	4% (1)	0
Diarrhea	0	11% (3)	4% (1)
Dysuria	0	4% (1)	0

Adverse Event	Placebo	MDMA	Open Label
	x/16 (N = 8)	x/28 (N = 15)*	x/23 (N = 12)†
Epigastric burning	0	0	9% (1)
Fatigue	13% (2)	13% (4)	9% (2)
Feeling hot	0	7% (2)	0
[PTSD] Flashback	6% (1)	0	0
General body pain	6% (1)	4% (1)	13% (2)
Generalized muscle aches	0	0	4% (1)
Head tightness	0	4% (1)	0
Headache	0	4% (1)	0
Irritability	0	4% (1)	0
Muscle tightness	6% (1)	7% (2)	4% (1)
Myoclonic jerks	0	4% (1)	0
Nausea	0	4% (1)	0
Neck pain	6% (1)	0	4% (1)
Neck tightness	0	4% (1)	0
Nocturia	0	4% (1)	0
Numbness in face	0	4% (1)	0
Palpitations	0	0	4% (1)
Panic attack	0	4% (1)	0
Shoulder pain	0	7% (2)	4% (1)
Sinus pressure	0	4% (1)	0
Stomach burning sensation of	0	4% (1)	0
Streptococcal sore throat	0	4% (1)	0
Teeth chattering	0	0	4% (1)
Teeth grinding	0	4% (1)	0
Tightness in jaw	0	7% (2)	0
Upper respiratory infection	6% (1)	4% (1)	9% (2)
Urinary tract infection	0	0	4% (1)
Visual disturbance	0	7% (2)	4% (1)
Vomiting	0	4% (1)	0

Relationship to study drug assessed prior to unblinding for randomized sessions, with only events reported in people who received MDMA presented here. Percentage = number of events / (number of drug administration sessions x number of participants).

* 15 participants took part in experimental session 1; two dropped out after first session and 13 took part in experimental session 2.

† 7 participants took part in two open-label sessions, and 4 of 7 took part in a third open-label session. 5 participants took part in open label session after receiving MDMA during Stage 2

Table 5b: Unexpected Adverse Events* that were Possibly or Probably related to MDMA OR Within Seven Days of Drug Administration for Randomized Sessions

Placebo			**MDMA**		
Adverse Event	% Reporting	# Subjects	Event	% Reporting	# Subjects
	x/16	N = 8		x/28	N = 15
Fatigue	**13%**	**2**	**Fatigue**	**13%**	**4**
Back muscle spasms	6%	1	Back muscle spasms	4%	1
Muscle tightness	6%	1	**Muscle tightness**	**7%**	**2**
Upper respiratory infection	6%	1	Upper respiratory infection	4%	1
General body pain	6%	1	General body pain	4%	1
Burning leg	6%	1	Burning finger	4%	1
Throat tightness	6%	1	Neck tightness	4%	1
Right upper quadrant pain	6%	1	**Shoulder pain**	**7%**	**2**
Facial pain	6%	1	Numbness in face	4%	1
Neck pain	6%	1	Asthenia	4%	1
Knee pain	6%	1	Back pain	4%	1
Calf pain	6%	1	Blistering of mouth	4%	1
Musculoskeletal chest pain	**19%**	**2**	Blurred vision	4%	1
Memory disturbance	6%	1	Concentration ability impaired	4%	1
Anxiety	**19%**	**2**	Derealization	4%	1
[PTSD] Flashback	6%	1	Detachment	4%	1
Low mood	6%	1	Diarrhea	**11%**	**3**
Itchy skin	6%	1	Dysuria	4%	1
*Events were coded using MedDRA version 12 (March 2009) using lower level terms. Events listed as number of times reported per session, and as number of participants reporting during two experimental sessions.			Appetite absent	4%	1
			Feeling hot	7%	2
			Head tightness	4%	1
			Headache	4%	1
			Irritability	4%	1
			Myoclonic jerks	4%	1
			Nausea	4%	1
			Nocturia	4%	1
			Panic attack	4%	1
			Sinus pressure	4%	1
			Stomach burning, sensation of	4%	1
			Streptococcal sore throat	4%	1
			Teeth grinding	4%	1
			Tightness in jaw	**7%**	**2**
			Visual disturbance	**7%**	**2**
			Vomiting	4%	1

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) [286], the Paced Auditory Serial Addition and Subtraction Task (PASAT) [287, 288] and the Rey Osterreith figure [289]. 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. At baseline, there was no difference in RBANS total scores, $t(1, 19) = -1.75$, $p. > 0.05$ ($p. = 0.09$), and two months after second experimental session, $t(1, 19) = -0.815$, $p. > 0.05$ ($p. = 0.425$). Baseline PASAT Trial 1 and Trial 2 percentage scores did not differ between MDMA and placebo groups: Trial 1 $t(1, 19) = -1.17$, $p > 0.05$ ($p. = 0.258$), Trial 2 $t(1, 19) = -0.016$, $p. >0.05$ ($p. = 0.98$). Two months after the second experimental session, MDMA and placebo subjects did not perform significantly differently on either the easier Trial 1, $t(1, 19) = -1.53$, $p. > 0.05$, $p. = 0.142$, or the harder Trial 2 $t(1, 18) = 0.146$, $p. > 0.05$ ($p. = 0.89$). At baseline, Rey-Osterreith 30-second recognition scores for people assigned to MDMA and placebo were not significantly different, $t (1, 18) = -0.235$, $p. > 0.05$ ($p = 0.82$) and two months after the second experimental session, there were still no differences between people assigned to either condition, $t(1, 18) = -1.23$, $p > 0.05$ ($p. = 0.24$).

Table 6a: 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 6b: 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 6c: 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

Analyses of the Clinician Administered PTSD Scale (CAPS) [290, 291] 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.

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).

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).

These findings are suggestive of an effect of MDMA in combination with psychotherapy in reducing PTSD symptoms. 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.

8.3 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, increasing empathy and prosocial feelings. On the basis of narrative reports and an initial study 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.

MDMA shares some effects with psychostimulants, such as increased energy and positive mood and increased blood pressure and 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. 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. It is metabolized in the liver by several enzymes. It is likely that active doses of MDMA saturate CYP2D6 function. The enzymes 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 2010, it has been administered to approximately 494 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 and Switzerland. Two sponsor-supported studies have completed investigations of MDMA-assisted psychotherapy in people with PTSD, and another study is investigating 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.

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, considering the millions of users taking ecstasy 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 AE to occur in this population. In addition to hyperthermic syndromes, other rare AEs 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. 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.

Side effects of MDMA are modest and generally have not been associated with serious discomfort by healthy volunteers in previous studies. Commonly reported side effects 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.

9.2.3.1 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. 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 occasionally 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 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.

9.2.3.2 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 MDMA (approximately 5% per trial) have had elevations above a cut-off of at least 140/90 mmHg. Tables 2a to 2d 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.

9.2.3.3 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, 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.

9.2.3.4 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. 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.

9.2.3.5 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.

9.2.3.6 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. 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.

9.2.3.7 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. 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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