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# A REVIEW ON INVESTIGATORS BROCHURE'S

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***Abstract :*** The Multidisciplinary Association for Psychedelic Studies (MAPS) is a U.S.-based non-profitresearch and educational organization that supports research into the therapeutic potential of hallucinogenic compounds and cannabis. MAPS is working to obtain approval for the prescriptionuse of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy inpatients 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 andclinical 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 MDM

***IndexTerms*** Attention Deficit Hyperactivity Disorder
Adverse Event(s)
Alanine aminotransferase
Acute Myocardial Infarction
Aspartate aminotransferase
Beck Depression Inventory
Clinician Administered
Central Nervous System

## 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 , 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 ,he and his colleagues provided initial reports of its pharmacology and effectsin humans MDMA was found to robustly influence human emotional status in a unique way without notably effecting physiological functions, such as visual perception or cognition

Shulgin and Nichols were the first to report on the effects MDMA in humans . 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, andposttraumatic stress disorder .During the early 1980s, increasing numbers of people began usingMDMA, sold as "Ecstasy" outside of therapeutic contexts .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 thesame contexts . To date, MDMA has been administered to over 494 individuals for research purposeswithout the occurrence of drug-related Serious Adverse Events (SAEs.Placebo-controlled Phase1 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 . 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, 94subjects participated in research studies not supported by the Sponsor. Studiesin healthy volunteershave investigated the acute and sub-acute subjective, psychological, physiological and neuroendocrine effects of MDMA. Initial studies in the 1990s examined the physiological effects ofMDMA 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 appearsfavorable for subjectswho are exposed to the highest dose of MDMA used in MAPS clinical trialprotocols 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 trialsare warranted.[1]

*Physical, Chemical, and Pharmaceutical Properties and Formulation*

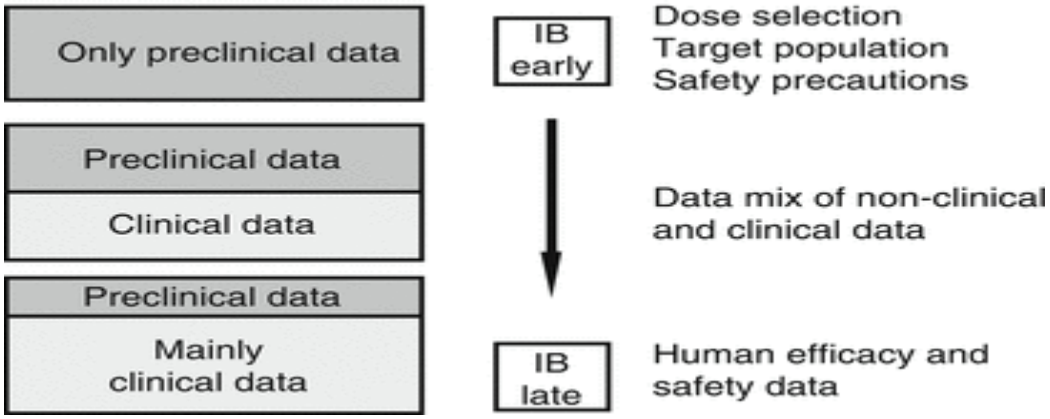
MDMA is structurally similar to amphetamines and mescaline. MDMA, also known as 3,4- methylenedioxy-n-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula of $C_{11}H_{15}NO_2$. It was first synthesized as a precursor of a haemostatic drug calledmethylhydrastinin as a phenylisopropylamine derivative of safrole, an aromatic oil found in sassafras, nutmeg, and other plants . MDMA is a chiral molecule, possessing two enantiomers,S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA . All research in humans to date and themajority of nonclinical studies have used racemic MDMA, or an admixture containing equal amounts of both enantiomers. Studies of drug discrimination in rodents and self-administration in primates suggest that not only do the enantiomers produce different effects, but that there may be some synergy between the two. It seems that R(-)-MDMAmay 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 . 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 .

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 . 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 The most recent analysis of drug stability and purity conducted on February 2, 2010 confirmed that this MDMA is 99.9% pure with no detectabledecomposition.

For Sponsor-supported studies, MDMA in the form of white crystalline powder is compoundedwith inert material into capsules. The capsules are stored in sealable containers placedwithin 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 doseis 125mg, which is equivalent to 1.25 mg/kg (100kg) to 2.6 mg/kg (48kg) for the initial dose. Theoptional supplemental dose of 62.5 mg is equivalent to 1.3 mg/kg (100kg) to 2.6 mg/kg(48kg).[2]




*Nonclinical Studies 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 (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 ofactivity on these receptors is low in comparison to monoamine transporters Recent *in vitro* studies suggest that MDMA inhibits norepinephrine uptake more strongly than dopamine uptakeand that MDMA does not have as strong an affinity for the dopamine transporter as methamphetamine 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 combination with other drugs or at high doses MDMA mayprovokeserotonin syndrome, a suite of specific signs and symptoms that can require intervention .

*Pharmacology and Product Metabolism in AnimalsPharmacology 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 Investigations of the pharmacology, functional effects, and toxicityof MDMA in animals have generally included injections of large and often repeated doses of MDMA in an attempt to produce human-equivalent doses . Recent reports re-examiningthese effects have questioned the applicability of interspecies scaling models for MDMA and supported nonlinear pharmacology. A study directly comparing MDMA pharmacokinetics in humansand 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. Bothspecies exhibited

nonlinear pharmacokinetics, and it appears that monkeys and humans exhibit similar plasma MDMA levels after receiving the same dose of MDMA . An investigation in rats also demonstrated nonlinear pharmacokinetics in that species as well, finding that human-equivalentdoses of MDMA in rats are close to or identical to those in humans, and drug half-life is rapid.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 offindings in nonclinical studies employing these dosing regimes. nonlinear pharmacokinetics, andit appears that monkeys and humans exhibit similar plasma MDMA levels after receiving the same dose of MDMA . An investigation in rats also demonstrated nonlinear pharmacokinetics inthat 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.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 . MDMA probably stimulates $5HT_{1A}$ receptors indirectly through serotonin release, though it is

possible that MDMA may also act as apartial $5HT_{1A}$ antagonist in some brain .Findings from other studies suggest that it sharesqualitieswith $5HT_{1A}$ agonists. Early studies in rodents suggest that $5HT_{1A}$ receptors reduce anxiety and aggression, and some drug discrimination studies suggest that the $5HT_{1A}$ agonist 8- OH-DPAT

partially or fully substitutes for MDMA . Administering a $5HT_{1A}$ antagonist attenuates the prosocial behavior of rats, measured by preference to lie adjacent to each other, possibly becauseit prevents elevation in oxytocin . At least some direct or indirect effects of MDMA on serotoninreceptors may cause changes in GABA uptake in the ventral tegmental areaof rats [3].

*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 . Some of the increased gene transcriptsare associated with monoamine release . Investigations with serotonin transporter knockout micesuggest 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 thecortex and hypothalamus . Increases in transcripts of genes regulating extracellular signaling in Endocrine

*Effects in Animals*

In rats, large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin , 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 proc A study of isolated rat hypothalamus reported arginine vasopressin (AVP) and oxytocin release after administration of MDMA and its metabolite HMMA . A recent study using 1-3 mg/kgdosesfound 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 .

*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 . Rats given lower doses of MDMA exhibited increased anxiety in the elevated plus maze , while rats given higher doses exhibited reduced anxiety on the maze. Rats given higherdoses 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 ("A study of isolated rat hypothalamus reported arginine vasopressin (AVP) and oxytocin releaseafter administration of MDMA and its metabolite HMMA . A recent study using 1-3 mg/kgdoses 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.all signs of rodent serotonin syndrome [109]. MDMA produces some repetitive behaviorin 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 . However, it isnotable that a recent publication failed to find thigmotaxis in rats given 5 mg/kg MDMA . In contrast, rhesus monkeys do not exhibit increased locomotor active[4].

*Toxicology 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 . Studies inrodents and primates suggest that MDMA could damage serotonin axons and cause neurotoxicity
. However, the majority of these studies employed large doses ofMDMA that overestimatedhuman-equivalent doses. It now appears that lower doses of MDMA donot reduce brain serotonin . Monkeys allowed to self-administer MDMA for an 18-month period had noreductions in brain dopamine, slight reductions in brain

serotonin, and no chemical

markers of neuronal injury . Rats receiving lower doses of MDMA also fail to exhibit signs ofneurotoxicity . 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[5] .

*Self-Administration in Animals*

Mice, rats, and monkeys will self-administer MDMA, indicating that MDMA has rewarding properties in animals . Monkeys choose to self-administer MDMA in doses equivalent to or onlyslightly higher than doses used by humans . but they reduced their MDMA intake overtime.
While monkeys will work hard to obtain MDMA, they will work harder to obtain other psychostimulants, such as cocaine or methamphetamine . Taken together, these results suggestthat the abuse liability of MDMA is moderate[6].

*Effects in Humans*

Evidence exists for intentional human use of MDMA as early as the late 1960s , and there are records of a police seizure of MDMA in the early 1970s . Shulgin and Nichols were the first to report on the effects of MDMA in humans . In the 1970s, psychotherapists used MDMA- assisted psychotherapy to treat anxiety, depression, and PTSD . Legal therapeutic use continued until its placement in US Schedule 1 in 1985 . Estimates indicate that 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling . A few uncontrolled human studies of MDMA occurred in the 1980s , 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 . 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.The Sponsor is currently planning future clinical trials based on the results of these two pilot studies[7].

*Pharmacology and Product Metabolism in HumansPharmacology in Humans*

Many researchers categorize MDMA as belonging to a unique class of drugs referred to as the entactogens . Entactogens are reported to produce changes in mood and social interaction as wellas feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens , but it also appears to share qualities with a small number of pharmacologically related compounds, such as methylenedioxyethylamphetamine (MDE) . Retrospective reports and surveys have assessed the social cognitive effects of MDMA or ecsta . To date only two controlled studies have sought to measure these effects . 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.

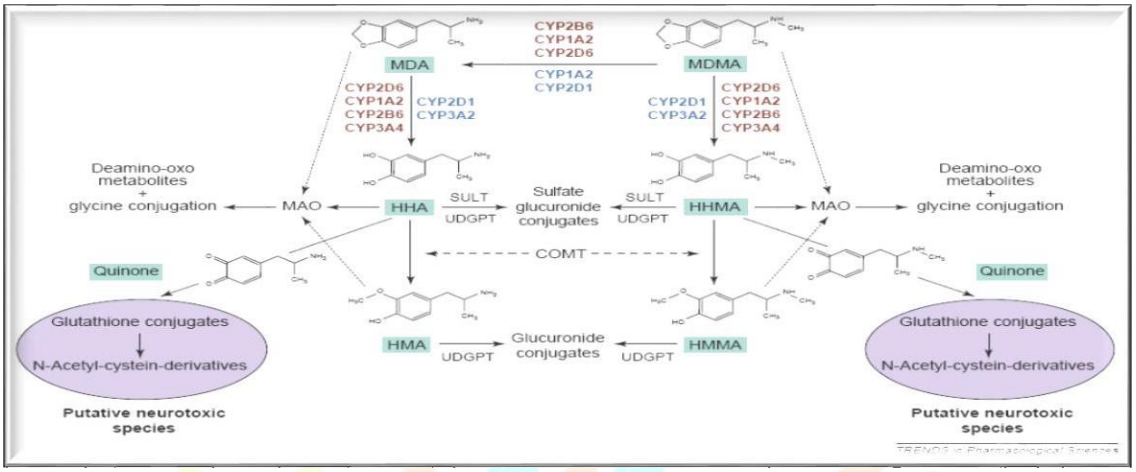
Estimates from animal data suggest the LD50 in humans is probably between 10 - 20 mg/kg . Typically, human trials have used doses between 1 and 2 mg/kg, with the design of the therapeutic studies using .Fixed dosing rather than adjusting dosing on a mg/kg basis, in order toachieve a moreconsistent subjective response between subjects. The pharmacokinetics of MDMA in humans havebeen 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 inproducing 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 MD. Pre-treatment or co-administration with SSRIsattenuates the effects of MDMA on mood and perception, without influencing specific effects suchas nervousness or excitability . Some researchers report that SSRIs attenuate MDMA- inducedincreases in heart rate and blood pressur while others report that SSRIs only attenuate elevated heart rate . 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 .

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 alongwith

1.5 mg/kg MDMA to 15 men only attenuated self-reported "dreaminess" and pleasantly experienced derealization after MDMA, without actually attenuating MDMA-related reductioninperformance on a task requiring visual attention .

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 moodand increased anxiety in humans . There are no reports examining the contribution of **Metabolism in Humans**




Metabolites of MDMA are summarized in Figure 1 Metabolites are primarily excreted as glucuronide and sulfate conjugates . Studies examining metabolism of 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates . Urinaryexcretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8 ± 23.8 moland 17.7% recovery . By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% .As was the case for maximal plasma values, urinary recoveries for MDMA andMDA were higher after a second dose of 100 mg MDMA than after an initial dose of 100 mg MDMA . 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 , suggesting that secondary metabolism of MDMA continues during this period.

*Physiological Effects in HumansEndocrine Effects in Humans*

MDMA acutely increases cortisol, prolactin, and adrenocorticotropic hormone concentrations ina dose dependent manner, whereas growth hormone is unchanged by up to 125 mg MDMA 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, and a dose of 100 mg MDMA given 24 hours after an initial dose stimulates a greater release of cortisol but not prolactin . A naturalistic study in clubgoers found a much greater elevation in cortisol afterecstasy use . In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was atrend 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 hourspost-drug . MDMA produces a robust increase in the neurohormone oxytocin , a finding first seen in a naturalistic study . 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 monoaminerelease, 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, andincreased cortisol in some circumstances may serve as a signal to seek affiliation or to increase positive mood[8] .

*Immunological Effects in Humans*

Studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects. 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 24hours after drug administration. These researchers also found that MDMA

decreased production ofpro- 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.

Changesof similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine . Because of their limited duration, these changesare not likely to have clinical significance beyond several days of possible increased risk of viral upper

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 . Furthermore, McCann and colleagues' surprisingly high overalldetection 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, meanecstasy 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

# *Investigator's Brochure template*

***Background for template:***

The purpose of the investigator's brochure (IB) is to provide the principal investigator sufficient safety or performance data from pre-clinical investigation(s) and/or clinical investigation(s) to justify human exposure to the investigational device specified in the investigational protocol. The IB shall be updated throughout the course of the clinical investigation as significant new information becomes available.

***Document Reference Number:***

***Name of Investigational Device:***

***Sponsor Name:***

***Sponsor Address:***

***Version No:***

***Date:***

**Revision History**

| Version Number | Date |
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**Authorised company signatory– Company Name** **Date**

these studies may be may not be applicable to estimations of the risk of three administrations of

*Effect on Homeostasis in Humans*

A number of case reports describe hyponatremia after uncontrolled, non-medical ecstasy use . Behavioral factors,

including vigorous exercise and excessive consumption of waterwithout an attempt to replace electrolytes, and an increase in the anti-diuretic hormones arginine vasopressinand 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[9].

*Reproductive and Developmental Risks in Humans*

Previous research supported a possible link between ecstasy use and birth defect , while an epidemiological study of a large cohort of pregnant women in England conducted in 2004 failed tosupport this link, at least in respect to a specific cardiac defect. However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey ofadrug-using population suggests that most women cease using ecstasy when they learn they are pregnant. As of early 2010, there have been no further investigations into the developmental effects of ecstasy use in humans[10]

*Toxicology*

**Neurotoxicity in Animals**

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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 monoaminerelease, 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, andincreased cortisol in some circumstances may serve as a signal to seek affiliation or to increase positive mood .

*Immunological Effects in Humans*

Studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects. 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 24hours afterdrug administration. These researchers also found that MDMA decreased production ofpro- 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.
Changesof similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine . Because of their limited duration, these changesare not likely to have clinical significance beyond several days of possible increased risk of viral upper

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 . Furthermore, McCann and colleagues' surprisingly high overalldetection 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, meanecstasy 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 ofthese studies may be may not be applicable to estimations of the risk

*Effect on Homeostasis in Humans*

A number of case reports describe hyponatremia after uncontrolled, non-medical ecstasy use . Behavioral factors, including vigorous exercise and excessive consumption of waterwithout an attempt to replace electrolytes, and an increase in the anti-diuretic hormones arginine vasopressinand 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.of threeadministrations of MDMA to participants in MAPS clinical trials.

**Reproductive and Developmental Risks in Humans**Previous research supported a possible link between ecstasy use and birth defect , while an epidemiological study of a large cohort of pregnant women in England conducted in 2004 failed tosupport this link, at least in respect to a specific cardiac defect. However, the authors also stated that exposure to MDMA in their samplewas too low to establish risk. An earlier survey of adrug-using population suggests that most women cease using ecstasy when they learn they are pregnant. As of early 2010, there have beenno further investigations into the developmentaleffects of ecstasy use in humans [15].

*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 . While a number of serious adverse events, including fatalities, have been reported after ecstasy use in unsupervised and uncontrolledsettings, these events are relatively rare given the prevalence of ecstasy use . These include hyperthermia, psychiatric problems, hepatotoxicity and hyponatremia. Drug- related serious

| | | | | | | |
|---|---|---|---|---|---|---|
| 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 ofappetite | 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% |

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, suchas rigorous exercise, lack of attention to somatic cues, and too little or too much hydration resulting in hyperthermia or hyponatremia . Hall and Henry address medical emergencies related to ecstasy use . 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 . 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 nonmedicaland recreational use, the researchers found it hard to establish a lethal dose . As is the case with fatalities, medical emergencies after ecstasy use are more likely to occur in men . Other serious adver`se 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

*Safety and Efficacy in Humans*

In recent years, clinical investigation of the safety and efficacy of MDMA-assisted psychotherapy has become more feasible . The first double blind, placebo controlled U.S. Phase1 study sanctioned by the FDA and supported by the Sponsor was conducted in 1994 . In this study, MDMA was found to be generally tolerable in a clinical setting. These results lead to the first Phase2 safety and efficacy study of low doses of MDMA-assisted psychotherapy in Spain on a small sample of women with chronic PTSD [16].

**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% |

*Summary of Data and Guidance for the Investigator*

MDMA is a psychoactive compound that some researchers refer to as an entactogen, a compoundthat affects mood and perception, increasing empathy and prosocial feelings. On thebasis of narrative reports and an initial study of MDMA in psychotherapy, the sponsor is investigating useof 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 notpermitted for use outside of research settings [17].

*Pharmacology*

The pharmacology of MDMA is complex and the chief mechanism behind its therapeutic effectsis 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

anuptake 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 ofMDMA 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 changesin 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 experiencedderealization, increased vigor, and anxiety. Recent reports suggest that it may also cause increasedfeelings of friendlinessand sociability. Acutely, MDMA transiently and selectively affects performance on tasks requiring attention and memory. Studies investigating the impact of MDMAon driving suggest that the drug does not strongly alter driving, but impairs some driving-related [18]

*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 studyparticipation, the sponsor and clinical investigator will follow the pregnancy to

outcome. 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 controlledsubstanceswithin research studies [19].

*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 lateris 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 ofincrease invital-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 [20]

*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 tofurther 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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