INVESTIGATOR'S BROCHURE

Investigational Product:	OPTI-MHCL (MDMA HCL) 3,4-methylenedioxymethamphetamine hydrochloride
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CONFIDENTIALITY STATEMENT

The information contained in this Investigator's Brochure is confidential and is provided to you as a potential investigator or consultant and shall be reviewed by either you or your designee(s), an affiliated ethics review committee, and relevant regulatory authorities.

Investigator's Brochure Amendments

DOCUMENT HISTORY	
Document	**Date**
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Investigator's Brochure Version 2.0. Major changes include: contact information of the manufacturer, validated manufacturing parameters for capsules, stability information for capsules drug products	22 November 2024
Investigator's Brochure Version 3.0. Major changes include: Updated clinical trial and safety information; dosing revised to reflect current clinical trial data, with supporting references. Revised in response to FDA comments: clarified regulatory status and Breakthrough Therapy Designation; consolidated and corrected mechanism of action (Sections 4.3, 5.1); removed nonclinical data without authorized reference	08 October 2026

List of Abbreviations

AE(s)	Adverse Event(s)
AESI(s)	Adverse Events of Special Interest(s)
AVP	Arginine Vasopressin
AUC	Area Under the Curve
BP	Blood Pressure
CAPS	Clinician Administered PTSD Scale
CBCT	Cognitive-Behavioral Conjoint Therapy
GMP	Good Manufacturing Practices
CNS	Central Nervous System
COMT	Catechol-O-methyltransferase
C-SSRS	Columbia Suicide Severity Rating Scale
DAT	Dopamine Transporter
DEA	Drug Enforcement Administration
DBP	Diastolic Blood Pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EKG	Electrocardiogram
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GD	Gestational Days
HDPE	High Density Polyethylene
HCl	Hydrochloride
HHA	3,4-Dihydroxyamphetamine
HHMA	3,4-Dihydroxymethamphetamine
HMA	4-Hydroxy-3-methoxy-amphetamine
HMMA	4-Hydroxy-3-methoxy-methamphetamine
IB	Investigator's Brochure
ICH	International Conference on Harmonization
LD50	Lethal Dose in 50% of Cases
LSD	d-Lysergic Acid Diethylamide
MAO-A	Monoamine Oxidase A
MAOI	Monoamine Oxidase Inhibitor

MAPS	Multidisciplinary Association for Psychedelic Studies
mCPP	meta-Chlorophenylpiperazine
MDA	3,4-Methylenedioxyamphetamine
MDMA	3,4-Methylenedioxymethamphetamine
mmHG	Millimeters of Mercury
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
nAChr	Nicotinic Acetylcholine Receptors
NET	Norepinephrine Transporter
PET	Positron Emission Tomography
PTSD	Posttraumatic Stress Disorder
SAE(s)	Serious Adverse Event(s)
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SERT	Serotonin Transporter
SNRI	Serotonin and Norepinephrine Uptake Inhibitor
SPECT	Single Photon Emission Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Event
TEAE	Treatment-emergent Adverse Event
WBC	White Blood Cell Count
5HT	Serotonin
8-OH-DPAT	8-Hydroxy-2-(di-n-propylamino) tetralin

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1. SUMMARY

A North American zeitgeist around the therapeutic potential of 3,4-methylenedioxymethamphetamine (MDMA) is currently underway. Clinical trials of MDMA-assisted therapy for patients with chronic psychiatric disorders such as post-traumatic stress disorder (PTSD), social anxiety, and anxiety related to terminal illnesses have already begun.

MDMA-assisted therapy combines traditional psychotherapy modalities with the administration of MDMA under direct observation by a trained medical professional. The intent of this Investigator's Brochure (IB) is to provide information on the pharmacology, safety, and efficacy of MDMA. The information presented in this IB summarizes results from published research studies of MDMA and case reports of people who use Ecstasy, unregulated material represented as containing MDMA.

The term PTSD was formally recognized in the Diagnostic and Statistical Manual (DSM) in version III published in 1980 [1]. It is characterized as a psychiatric disorder that may occur following a traumatic event such as military combat, violence, sexual assault, kidnapping, hostage taking, terrorism, torture, incarceration, natural/man-made disasters, serious medical emergencies, and accidents [1]. Studies estimate the lifetime prevalence of PTSD in the U.S. adult population is estimated between 6.1% and 9.2% [2]. Evidence based psychotherapies and pharmacotherapies exist but may be difficult to tolerate [3-5] and are ineffective for many individuals with PTSD. It is estimated 40 to 60% of patients remain symptomatic even after receiving treatment [5-7]. In addition, available pharmacotherapies used to treat PTSD may have problematic side effects and generally require long-term and/or consistent use to maintain effectiveness [4]. Modern treatment modalities are needed to better address the long-term needs of people with PTSD and MDMA-assisted therapy has the potential to serve as a tolerable treatment that requires only a handful of administrations with lasting treatment effects.

MDMA is structurally similar to, but functionally distinct from, amphetamines and mescaline. The effects of MDMA effects occur 30 to 60 minutes post consumption with peak effects appearing 75 to 120 minutes post consumption lasting approximately 3 to 6 hours, and an elimination half-life of active doses of MDMA being 7 to 9 hours [8-15].

MDMA is anxiolytic and acts primarily as a releaser of serotonin, norepinephrine, and dopamine via the monoamine transporters, with the greatest effect on serotonin (see Section 4.3) [18-22]. Subjective effects of MDMA can include increased compassion for self and others, reduced defenses, and fear of emotional injury, and making unpleasant memories less disturbing while enhancing communication and capacity for introspection [23-26]. These factors cumulate to provide the opportunity for a corrective emotional experience in the context of therapy. Many of the therapeutic effects of MDMA-assisted therapy are evident within a short period of treatment, often after the initial session.

Increased feelings of interpersonal closeness, changes in social perception, and reduced anxiety might make MDMA a suitable pharmacological adjunct to enhance therapy for treatment of anxiety disorders, such as PTSD, social anxiety, and anxiety associated with other conditions.
PTSD is a serious, chronic, life-threatening condition that afflicts a substantial number of individuals who are more likely to exhibit increased risk of suicide, psychiatric comorbidities, cardiovascular disease, and functional impairment. Those who suffer from PTSD are often insufficiently treated with available therapies. In clinical trials to date, MDMA has been well-tolerated and has reduced symptoms of PTSD. In summary, results

from clinical studies to date suggest a favorable risk/benefit profile among PTSD participants treated with a two to three- session MDMA-assisted therapy, which also included follow-up non-drug therapy sessions. Therefore, MDMA-assisted therapy might be a novel treatment option with the potential for significant clinical improvements.

2. INTRODUCTION

MDMA was first synthesized and patented by Merck in 1912 [27] and was rediscovered by the chemist Alexander Shulgin in 1976 [28]. Shulgin and colleagues provided the first reports of its effects in humans, finding that oral doses of 80 to 160 mg MDMA HCl produced a unique shift in emotional state [29, 30] without adversely affecting physiological functions or perception, such as visual perception or cognition [9, 11, 13, 14]. Reported effects included enhanced feelings of closeness to others, well-being and insightfulness [31-33]. During the 1970s and 1980s, MDMA was used to enhance individual, couples and group therapy for various psychological disorders, including moderate depression and anxiety, and was also reported to reduce physical pain secondary to certain cancers [32, 34-36]. However, no formal controlled clinical trials of safety and efficacy were conducted during this period [32, 37].

During the early 1980s, MDMA was being sold as 'Ecstasy' outside of therapeutic contexts and being used by a vastly increasing number of people [38]. In the U.S., an estimated 6.8% of people aged 12 years and above reported using 'Ecstasy' (material represented as containing MDMA) at least once in their lifetimes [39], and an estimated 4% of Europeans aged 15 to 64 reported lifetime Ecstasy use [40]. MDMA was added to the list of Schedule I controlled substances in the U.S. in 1985, meching it as a drug with a high potential for abuse and no accepted medical use [41, 42].

Classification as a Schedule I controlled substance, combined with the early research in animals and recreational users, hampered clinical research for medical uses of MDMA until the 1990s. Adverse reports following use of Ecstasy have raised safety concerns regarding MDMA administration, including hyperthermia [43-45], changes in serotonin transporter (SERT) density, and impaired memory and executive function [46-50]. However uncontrolled studies of Ecstasy use and nonclinical animal studies at doses significantly greater than the therapeutic dose range of MDMA yielded findings that are open to an array of interpretations [51, 52]. Most publications on Ecstasy users have been retrospective reports in polydrug-users who are using drugs of unknown purity and quality [53, 54].

Initial human studies from the 1990s focused on physiological effects of MDMA from a safety perspective, and current investigations have examined the effects on attention, prosocial effects, memory and brain activity, and human drug discrimination. An early study indicated that MDMA-assisted therapy could be conducted safely in people with chronic PTSD who had no success with pre-existing treatments [55]. This was demonstrated in a chronic, treatment-resistant PTSD sample [56], which demonstrated long term improvement in PTSD severity. In this study, MDMA had no deleterious effects on cognitive function or safety pharmacology laboratory results when given on two occasions, spaced 1 month apart. In addition, placebo-controlled Phase 1 clinical trials confirmed that the active doses of MDMA produce an easily controlled state characterized by euphoria, increased well-being, sociability, self-confidence, extroversion, transient increases in anxiety, and minor alterations in perception [9, 11-13, 57-61]. Other areas of interest for MDMA-assisted therapy have extended to treating anxiety related to life threatening illnesses, certain adults with autism spectrum disorder who experience high social anxiety, and populations with tinnitus. MDMA is also of interest

for investigating serotonin and norepinephrine system in the brain and using it to explore potential states of dysfunction.

2.1 Manufacturer Contact

Optimi Labs Inc. is an innovator and leader in supporting and expanding the safe, accessible, and evidence-based use of psychedelic-assisted psychotherapies. Optimi Labs Inc. has established itself at the forefront of psychedelic therapeutic development and as a center of excellence for product research and development, and as a supporting arm for psychedelic therapy clinical trials. Optimi Labs Inc. has a Dealer's License from Health Canada for the purchase and production of psychedelics, including MDMA and psilocybin.

Dr. Preston Chase, Ph.D., Chief Scientific Officer
preston@optimihealth.ca

2.2 Product Development Contact

Optimi Health Corporation of Vancouver, British Columbia, Canada, is aiming to develop a synthetically produced, GMP compliant MDMA product. This Investigator's Brochure includes publicly available data relevant for the 40 mg and 60 mg OPTI-MHCL (MDMA HCl) capsules which are produced and supplied by Optimi Labs Inc (a subsidiary of Optimi Health Corporation).

Dane Stevens, Founder and Director, CEO, Optimi Health
dane@optimihealth.ca

2.3 Research Contact

The research contact is Dr. Preston Chase, Ph.D., Chief Scientific Officer, preston@optimihealth.ca.

2.4 Name(s) of Investigational Product

OPTI-MHCL (3,4-methylenedioxymethamphetamine hydrochloride) is present as 2 capsule strength with 40 mg and 60 mg MDMA HCl per capsule for oral administration.

2.5 Active Ingredients

MDMA is presenting as hydrochloride salt (3,4-methylenedioxymethamphetamine hydrochloride) which is a white or off-white powder soluble in water. It is stable over extended periods in aluminum blister strips or in HDPE bottles, in dark storage at room temperature.

2.6 Pharmacological Class

MDMA is a ring-substituted phenethylamine classified as an entactogen; it acts primarily as a monoamine releaser (see Section 4.3).
MDMA is controlled under Schedule I of the Controlled Drugs and Substances Act.

2.7 Rationale for Performing Research with the Investigational Product

A Phase 3 clinical trial in 2020 supported the efficacy and safety of MDMA-assisted therapy for treatment of PTSD. In this randomized, double-blind, placebo-controlled, multi-site study, participants with severe PTSD were treated using divided doses of 80 mg to 180 mg MDMA HCl. This pivotal phase 3 study supported that MDMA-assisted therapy was generally well tolerated in patients with PTSD. Additionally, the trial's primary and secondary endpoints of reduced PTSD symptom severity and decreased functional impairment gave additional support of MDMA being a viable new treatment for patients [62].

The second, multi-site, phase 3, randomized, double-blind, confirmatory study in 2022 evaluated the efficacy and safety of MDMA-assisted therapy versus placebo with identical therapy in participants with moderate to severe PTSD. Findings of this study replicated and extended the results observed in the previous phase 3 study, through an ethno-racially diverse population with general consistency across endpoints. MDMA-assisted therapy significantly attenuated PTSD symptomology versus placebo with therapy, as measured by a reduction in CAPS-5 total severity score from baseline to 18 weeks [63].

MDMA is not approved by the FDA, Health Canada, or other major regulatory agencies for any therapeutic indication and remains an investigational drug. In 2017, the FDA granted Breakthrough Therapy Designation (BTD) to MDMA-assisted therapy for PTSD based on Phase 2 data [64]; BTD is intended to expedite development and review of a drug and does not constitute approval or a determination of safety or efficacy. With the two Phase 3 trials (MAPP1 and MAPP2) reporting statistically significant reductions in PTSD symptom severity compared with placebo-assisted therapy the research environment continues to grow steadily.

As the need of future clinical trials to investigate the support for MDMA assisted therapy continues to expand, demand has increased for pharmaceutical-grade MDMA. This encouraged Optimi Labs Inc. to develop a GMP-compliant MDMA product to supply the broader research community for PTSD clinical trials.

2.8 Importance of a Supportive Set and Setting Protocol

By addressing the set (the emotional/cognitive/behavioral state/mindset and expectations of study participants just prior to psilocybin exposure) and setting (the physical environment in which the exposure occurs) of the experience, the risk of the subject reporting MDMA-related events, such as vigorous exercise, lack of attention to somatic cues, hyperthermia and/or hyponatremia, can be reduced. This approach generally incorporates three components: 1) preparation, 2) drug session, and 3) post session meetings to integrate the classic hallucinogen experience.

2.9 Intended Use(s)

Currently, the prospective drug formulation is intended for use under research conditions only and with supervision of a healthcare professional. Upon demonstration of the safety and efficacy of the product, and Health Canada-granted marketing approval, the product is intended to be distributed by healthcare professionals through prescription or special access programs only.

MDMA is a psychoactive compound that affects mood, perception, and increases prosocial feelings. The prospective drug is being investigated to assess the safety of MDMA when administered to healthy

participants and as an adjunct to therapy for treating PTSD, MDD, and end-of-life anxiety in palliative care patients.

There are no indications specific for weight or sex. The prospective drug is indicated for use on adults over the age of 18. The product users are largely expected to be adults either with or without any of the potential diagnoses listed above.

2.10 General Approach for Evaluating the Investigational Product

The current clinical evaluation plan will be carried out to collect pertinent pre-market data required to support the safety and efficacy of the MDMA product. The current clinical data suggest that MDMA -assisted therapy is generally well tolerated. Proper preparation and follow-up support will reduce the difficulties participants might have with acute or sub-acute reactions. Critical performance consideration to align with the proposed indications specific to the clinical investigation include:

- Adequate and well-designed clinical study protocol that describes how adverse events or serious risks are mitigated during the trial.
- Excluding people who are diagnosed with bipolar affective disorder type 1 or with psychotic disorders.
- Study design controlling for functional unblinding and expectancy bias, using blinded raters, and expectancy questionnaires.
- Informed consent clearly describes that subjects may experience changes in perception, cognition, and judgment that persist for many hours, as well as increased vulnerability and suggestibility during the treatment session.
- Subjects are not placed at an unreasonable and significant risk of illness or injury for as long as 12 hours after receiving treatment with MDMA.
- Preparatory Sessions of non-drug therapy before the dosing session.
- Creating an atmosphere of trust during the dosing session.
- Close monitoring.
- Phone contact with participants during the week after the dosing session.
- Integrative Sessions.

3. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1 Physical, Chemical, and Pharmaceutical Properties

MDMA is the short form of the name 3,4-methylenedioxymethamphetamine. The International Union of Pure and Applied Chemistry (IUPAC) nomenclature is (RS)-1-(benzo[d][1, 3]dioxol-5- yl)-N-methylpropan-2-amine, and the United States Adopted Name (USAN) is midomafetamine hydrochloride. It is structurally similar to amphetamines but with a ring-substituted phenethylamine also known as methylenedioxymethamphetamine. MDMA, also known as 3,4-methylenedioxy-N-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula $C_{11}H_{15}NO_2$.

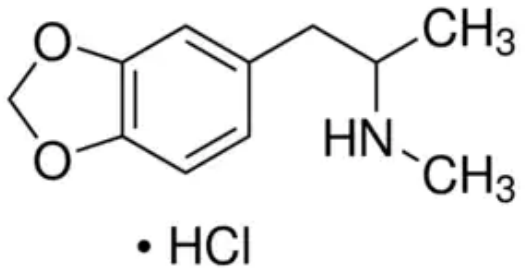


Figure 1. Chemical structure of 3,4-methylenedioxymethamphetamine hydrochloride.

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [64, 65]. Research in humans to date, and the majority of nonclinical studies have used racemic MDMA, or an admixture containing equal amounts of both enantiomers. A recent clinical trial in 24 healthy participants compared S- and R-MDMA to the racemic mixture. It found that S(+)-MDMA had stronger stimulant effects, which the authors attribute mainly to the enantiomer's higher potency. R(-)-MDMA, not S-MDMA, lasted longer in participants' systems (half-life of 12–14 h vs. about 4 h). This is due to R-MDMA blocking CYP2D6 and thus preventing its own metabolism, as well as that of S-MDMA when given as the racemic mixture. They concluded that the R and S enantiomers don't act very differently in the body and they differ mainly in potency. They found no evidence that either enantiomer offers an advantage over the racemic mixture [66].

The current manufacturing process produces racemic MDMA. MDMA doses in the Phase 2 and 3 studies have been therapeutic doses ranging of 120 mg to 180 mg MDMA HCl rather than dosing by body weight as previous studies have done [8]. MDMA (as hydrochloride salt) in the form of white to off-white crystalline powder is compounded with the excipient mannitol. The blend is then encapsulated in hard gelatin capsules of 40 mg and 60 mg MDMA HCl. Placebo to match consists only of mannitol. All human studies to date have used MDMA HCl, instead of MDMA free base, likely due to the salt being easier for oral administration and shelf storage.

MDMA HCl does not require special conditions for storage. Drug product capsules are produced under GMP. The capsules are packaged in HDPE bottles. The containers are typically placed in a safe or vault at controlled room temperature in a dry, clean, well- ventilated space at temperatures between 18 to 25°C. Short-term

excursions between 15 to 30°C are allowed based on available stability data. Drug product capsules are currently studied under ICH Q1A(R2) complaint stability programs for one year from the date of manufacture. Contact the manufacturer for future stability information.

As a Schedule I controlled substance, MDMA is stored and handled in compliance with relevant federal, provincial, and local regulations. License holders are responsible for administration and dispensing of the MDMA for approved uses only. They are responsible for ensuring that it is stored securely in accordance with the requirements of Office of Controlled Substances (OCS) Canada and other relevant regulatory authorities.

Chemical properties of MDMA:
CAS Registration Number: 42542-10-9
IUPAC Name: (RS)-1-(benzo[d][1, 3]dioxol-5- yl)-N-methylpropan-2-amine
Molecular Formula: $C_{11}H_{15}NO_2$
Molecular Weight: 193.246 g/mol

3.2 Description of Investigational Drug Substances and Formulations

For use in clinical studies, the drug product and placebo are provided in blue and white gelatin capsules for oral dose administration.

The 40 mg MDMA HCl capsule is presented as a Size 1 hard gelatin capsule containing 272 mg of a white powder blend that is composed of MDMA HCl drug substance and mannitol. The 60 mg capsule is presented as a Size 0 hard gelatin capsule containing 385 mg of a white powder blend of MDMA HCl drug substance and mannitol.

The 40 mg matching placebo capsule is presented as a Size 1 hard gelatin capsule containing 272 mg of mannitol as white powder. The 60 mg matching placebo capsule is presented as a Size 0 hard gelatin capsule containing 385 mg of mannitol.

PRODUCT DESCRIPTION:		MDMA HCl (3,4-methylenedioxymethamphetamine hydrochloride)	
EXCIPIENT LIST:		Mannitol	
ACTIVE INGREDIENT PER FORMULATION:		MDMA HCl – 40 / 60 mg	
DOSAGE FORMAT:	Hard gelatin capsule	**CAPSULE SIZE:**	1 / 0
TOTAL FILL WEIGHT:		OPTI-MHCL40: 273 mg OPTI-MHCL60: 386 mg	
CAPSULE DESCRIPTION:		Blue & white colored, gelatin capsules	
FILL PHYSICAL DESCRIPTION:		White powder	

3.3 Storage and Handling

The capsules will be packaged into labeled HDPE bottles. Bottles should be stored securely at controlled room temperature. The natural color of the capsules and containment within the bottles are sufficient for filtering out light and mitigating light-based degradation for the study product.

Given that MDMA is controlled substance, only specific study staff will be provided designated access to the investigational product, which must be handled in accordance with applicable Canadian drug regulations.

Both the MDMA and placebo capsules will be packaged individually into high-density polyethylene bottles and labelled with appropriate participant identification code to maintain randomization and blinding, as applicable. Bottles must be stored at controlled room temperature, protected from light and moisture, in a locked, secure location at the research site, and in accordance with Controlled Drugs and Substances Act (Canada). Only delegated and pre-defined study staff will have access to the investigational products.

4. NONCLINICAL STUDIES

4.1 Introduction

MDMA was first synthesized by the E. Merck company in Germany and patented in 1914 as a precursor for other compounds of possible commercial interest [67]. The first report of its psychoactive action in humans was by Shulgin and Nichols (1978) although the effects encountered are not detailed. Finally in the 1980s reports started to appear on its possible therapeutic properties with papers detailing its use in psychotherapy. It was reported to increase patient self-esteem and facilitate communication [68-70]. However, in 1985 the US Drug Enforcement Administration classified MDMA as a Schedule 1 drug due to its high abuse potential, lack of clinical application, lack of accepted safety under medical supervision and evidence that its major metabolite 3,4-methylenedioxyamphetamine (MDA) induced degeneration of 5-hydroxytryptamine 5-HT neurons in brain. Therefore, possession of the drug was made illegal soon after in the USA, Canada, and many other countries.

Over the past decades a substantial number of studies have been conducted on the pharmacology of MDMA in laboratory animals. These investigations have provided detailed and valuable information on the mechanisms involved in producing the acute adverse effects of MDMA in experimental animals, particularly the body temperature changes [71] and the long-term neurotoxic effects of the drug in the brain [51, 72, 73].

4.2 Non-clinical Pharmacology

Findings from nonclinical animal and *in vitro* research are presented. Investigations of the non-clinical pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA that are not human-equivalent doses. Studies of MDMA have been conducted in primates and rodents. Primate species studied include baboon, macaque, rhesus monkey, and squirrel monkey, and rodents include mice and rats. Studies of circadian rhythm have occurred in hamsters [74]. Beginning in the mid-2000s onwards, reports re-examining these effects have questioned the applicability of allometric interspecies scaling models for MDMA [51, 75, 76].

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor. Its prominent serotonergic effects differentiate it from amphetamine and methamphetamine, which primarily act on dopamine and norepinephrine [18, 77]. MDMA also has a complex profile from a pharmacokinetics perspective and has been demonstrated in multiple animal models to follow nonlinear pharmacokinetics, with increased doses resulting in disproportionate increase in exposure to the parent compound. Additionally, MDMA exhibits pharmacodynamic drug interactions with other drugs commonly used in psychiatry.

4.3 Mechanism Of Action

MDMA acts principally at the presynaptic monoamine transporters that normally clear neurotransmitter from the synaptic cleft, rather than through direct receptor agonism. It interacts with all three transporters but binds with highest affinity to the serotonin transporter (SERT), with at least ten-fold lower affinity at the norepinephrine (NET) and dopamine (DAT) transporters [72]. This selectivity distinguishes MDMA from most amphetamines, which act predominantly at the DAT, and is pharmacologically consequential: MDMA's more pronounced effects at the SERT than the DAT underlie its entactogenic effect profile and lower abuse liability [78].

Rather than simply inhibiting uptake, MDMA is itself transported into the nerve terminal, where it reverses the normal direction of transporter flux and drives non-exocytotic efflux of serotonin into the synapse [79]. In rats, in vivo microdialysis demonstrates a rapid, dose-dependent rise in extracellular serotonin, mirrored by a marked fall in brain tissue serotonin over the subsequent hours. Pretreatment with the uptake inhibitor fluoxetine largely abolishes this release, confirming that it is carrier-mediated [72]. MDMA also elevates striatal dopamine, but by a different route: the dopamine uptake inhibitor GBR 12909 augmented rather than blocked dopamine efflux in vivo, indicating that MDMA enters dopaminergic terminals by diffusion rather than via the transporter [72]. In synaptosomal preparations, MDMA releases norepinephrine with potency comparable to serotonin and greater than dopamine [72].

Two further intracellular actions amplify this release. Once inside the terminal, MDMA acts as a substrate at vesicular monoamine transporters, disrupting vesicular storage, and weakly inhibits monoamine oxidase, preferentially MAO-A [72, 78]. Both increase the cytosolic pool of neurotransmitter available for transporter-mediated efflux. MDMA additionally produces acute inhibition of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis, which contributes to the depletion observed after the initial release [72].

Direct receptor binding is comparatively weak but occurs at concentrations achievable in brain after typical doses. MDMA binds in the low micromolar range to 5-HT2, α2-adrenergic, M1 muscarinic and H1 histamine receptors, and behaves as a partial agonist of low intrinsic efficacy at the 5-HT2A receptor [72]. This weak 5-HT2A activity accounts for the low incidence of hallucinogenic effects and distinguishes MDMA from the classic psychedelics, whose effects depend on potent 5-HT2A agonism [78]. MDMA is also a ligand at trace amine-associated receptor 1 (TAAR1), which negatively modulates monoaminergic neurotransmission [80].

The behavioural consequences therefore arise largely from released serotonin acting at postsynaptic receptors rather than from MDMA itself. In mice, MDMA's prosocial effect required action at the serotonin transporter within the nucleus accumbens and depended on 5-HT1b receptor activation; it was reproduced by d-fenfluramine, a selective serotonin releaser, whereas its rewarding properties were mediated separately by

dopamine [81]. Oxytocin signalling is also implicated: oxytocin receptor antagonists block MDMA-induced prosocial behaviour in rats and mice, and in mice a single dose reopened a developmental critical period for social reward learning through oxytocin receptors in the same region [82].

4.4 Toxicology

MDMA has been studied in single-dose and repeat-dose toxicology studies [84, 85]. Genotoxicity has been evaluated in regulatory-compliant in vitro and in vivo test systems [88], and prenatal exposure has been examined in rats [87].

Independent nonclinical studies support that MDMA possesses abuse potential, but much less than structurally related compounds, such as amphetamine [89-92]. Overall, studies have shown MDMA was well tolerated with no mortality or significant toxicological findings after oral administration to rats (<150 mg/kg) and dogs (<9 mg/kg) when single-housed [84, 85].

A single-dose study of Sprague-Dawley rats, 10 rats per sex were exposed to 300 mg/kg p.o.. Of these, 40% per sex died, and 12 survivors were euthanized 3 days later [84]. The single-dose oral LD50 was estimated at 322 mg/kg, which is 6x higher than the LD50 for i.p. injection [93]. These findings show that MDMA administered orally at 300 mg/kg (approximately 100 to 150x the accepted human therapeutic dose), resulted in marked adverse clinical reactions, including death; with physiological and morphological changes in the kidney (hydronephrosis), and possible testicular tubular changes. No evidence of histologic brain damage was found in the survivors using standard histopathology assessments.

Single doses between 5 and 100 mg/kg have been administered in rodents. Single doses in this range have transient effects on serotonin depletion [51, 94-96], likely due to reversible inhibition of tryptophan hydroxylase [96-98], which prevents additional serotonin from being produced and released. A study of the long-term effects of a single dose of 5.7 mg/kg MDMA HCl on estimated SERT sites in the brains of squirrel monkeys reported reduced SERT sites in some frontal, temporal and parietal areas [99]. The plasma Cmax of 725 µg/L in squirrel monkeys was 3x greater than what is observed in humans after a single dose of 100 mg MDMA HCl [100-102].

In order to establish the Clinical Development Program for MDMA, 28-day repeat-dose general toxicity studies were conducted in both sexes of Sprague-Dawley rats (53 male, 52 female) (0, 10, 50, 100 mg/kg MDMA HCl oral gavage) and dogs (12 male, 12 female) (0, 3, 9, 15 mg/kg/day MDMA HCl oral dosing with gelatin capsules) [85]. The initial highest dose was set at 18 mg/kg/day but after the death of one female dog, the highest dose was subsequently reduced to 15 mg/kg/day. Dosing was once daily for 28 days. Both sexes of dogs administered 9 and 15 mg/kg/day of MDMA HCl and rats receiving 50 and 100 mg/kg/day gained less weight than controls and the 3 mg/kg/day group, with significant differences in food consumption observed as early as the first week which were no longer significantly different by the third week for the rats and the fourth week for the dogs. Gross observations at necropsy in the dog possibly related to MDMA included reduced testicular size for one of three dogs receiving 9 mg/kg/day and one of three dogs receiving 15 mg/kg/day and prostatic enlargement in two dogs receiving 15 mg/kg/day. No gross lesions were seen in the rats at necropsy. Blood chemistry and urinalysis values were unremarkable in the dog. Clinical pathology findings showing a trend to decrease with dose in the rat were urinary pH, blood urea nitrogen, glucose, creatinine (females), lactate dehydrogenase (females), and chloride, in contrast total white blood cell count (WBC) and phosphorus showed a trend to increase with dose. Histopathological examinations showed mild,

diffuse atrophy in the two dogs with reduced testicular size. Mild, focal atrophy was furthermore observed in the testes of one additional dog from the 15 mg/kg/day group. The two dogs with grossly enlarged prostates showed hyperplasia of the prostate. The silver stain for neurohistopathology was inconclusive in both the rat and the dog studies. These were interpreted as potentially MDMA-related effects as they were only seen in MDMA dosed animals and not in vehicle treated animals. In the rat, effects were observed in 5 of 10 male rats administered 100 mg/kg/day (none were observed in females). Although inconclusive, these potential effects were interpreted as vacuolated lesions apparent in the fiber tracts of the brainstem adjacent to the trigeminal nuclei. In the cerebrum of the dog, these effects included floccular changes of white matter, focal neural malacia and focal cellular infiltrates.

In a dose range study of Sprague-Dawley rats, oral toxicity was assessed in a 13-day increasing dose regimen [84]. The initial dose started at 25 mg/kg and was increased by 25 mg/kg on a daily basis until 300 mg/kg was reached. Adverse reactions were observed in all doses above 25 mg/kg and included hyperexcitability, uncontrolled urination, piloerection and bulging eyes. Tremors, muscle spasms, impaired movement, convulsions, and death were observed in the highest of dose levels, in the range of 150 and 300 mg/kg. Blood chemistry analyses suggested possible liver and kidney damage in animals receiving higher doses, however, gross pathology and microscopy found no treatment-related damage to the liver. The only renal change observed via microscope was mild to minimal hydronephrosis, which the researchers attributed to treatment-related polyuria (abnormally large urine production). Minimal tubular atrophy was seen in the testes of 3 of the 20 treated male rats, suggesting a possible relationship between high dose, repeated MDMA treatment and minimal testicular atrophy in the male rat. Gross pathology revealed reddened lungs and enlarged urinary bladders (most likely polyuria-related) in some animals and were deemed potentially treatment- related. Histopathological observations of brain tissue revealed no signs of brain damage in any of the treated rats.

Several studies have observed long-term changes in behavioral response in rats following doses of MDMA that have not produced loss in 5-HT content or loss of [3H]-paroxetine binding in any brain region examined. For example, Rodsiri et al. (2011) reported long-term disruption of novel object discrimination 2 weeks following 'binge-type' repeated low dose MDMA administration, but no loss of 5-HT in hippocampus, cortex or striatum [103]. Similarly, Fone et al. (2002) observed that MDMA administration to adolescent rats reduced social interaction and enhanced the subthreshold rewarding effect of cocaine at adulthood, despite an absence of 5-HT loss in cortex, hippocampus or brain stem or any alteration in [3H]-paroxetine binding [104]. The study of Bull et al. (2004) noted that MDMA pretreatment attenuated both the anxiogenic effect and the wet-dog shake behavior elicited by the 5-HT2A agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), suggesting that short term exposure to MDMA may cause a long-lasting alteration in 5-HT2A receptor function [105]. Again, this change was not accompanied by any alteration in [3H]-paroxetine binding.

One therefore must be aware that 5-HT concentration or [3H]-paroxetine binding may not be the only, or even the best, markers of neurotoxic-induced change. Long-term changes in function may be occurring, which are not directly due to 5-HT loss but could result from a long-term compensatory reinnervation or hyperinnervation of brain regions like the amygdala and hippocampus that regulate the response to environmental cues or to modifications in 5-HT receptor function such as a change in the 5HT2A sensitivity [105, 106].

4.5 Reproductive and Developmental Toxicity

Preliminary teratological studies in rats (N=12 per dose) given 0, 2.5, or 10 mg/kg MDMA (with correction factor for HCl salt) by gavage on alternate gestational days (GD) 6 to 18 found no abnormalities in gestational duration, litter size, neonatal birth weights, or birth defects (N=10 liters per dose), despite statistically significant reduction in maternal weight gain at 10 mg/kg [87]. These results are in contrast to physiological abnormalities resulting from prenatal methamphetamine and d-amphetamine exposure in mice and rabbits [107].

4.6 Safety Pharmacology

The pharmacology of MDMA is complex; it activates multiple signaling cascades in the body. Majority of pharmacology studies in the literature employed multiple dosing regimens to account for the shorter drug half-life in animals compared to humans, with doses ranging from 5 mg/kg to 20 mg/kg, via subcutaneous (SC), intraperitoneal (IP), oral/per os (PO), or gavage administration. Frequently, doses are administered at regular intervals of two to four times per day. Other regimens used these doses once daily for 5 or 7 days. Doses were selected through use of simple dose conversions or allometric scaling, a method of modeling human equivalent doses in other species [108].

4.7 Abuse Potential

Nonclinical studies support that MDMA possesses some abuse potential, though to a much lesser degree than amphetamine. This is based on a number of studies that have investigated the abuse liability of MDMA in animals through paradigms of drug seeking, drug discrimination, and withdrawal. Mice, rats, and monkeys self-administer MDMA, indicating that MDMA has rewarding properties in animals [109-112]; however, the rate and response-acquisition of self-administration is much lower than other drugs of abuse, such as cocaine or heroin. Rodent studies found that training attempts at self-administration required an increased training dose of 1.75 mg/kg for acquisition over a 5-week period [111, 113-115]. Research that used the ability of a drug to impact the rate of intracranial self-stimulation (ICSS) as a measure of abuse liability compared the impact of 0.32, 1, or 3.2 mg/kg MDMA HCl pretreatment in male and female rats. At the 3.2 mg/kg dose, MDMA increased responding for ICSS when the rate of responding for ICSS was low, and reduced seeking ICSS when rate of responding was very high in both sexes [89].
Physical dependence and drug withdrawal were investigated by treating rats with 10 mg/kg IP MDMA HCl twice daily for 5 days. When compared with rats trained to self-administer cocaine, MDMA-trained rats were less likely to return to self-administration after a period of abstinence [110]. Results in a study in mice showed that they did not exhibit aversive/dysphoric or anxiogenic behaviors after treatment, indicating that high doses of MDMA do not induce classical symptoms of physical dependence [89]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [109], but typically reduce their MDMA intake over time. While monkeys work hard to obtain MDMA, they work harder to obtain other psychostimulants, such as cocaine or methamphetamine [114, 115]. Taken together, results in animals suggest that the abuse liability of MDMA is low to moderate.

5. EFFECTS IN HUMANS

5.1 Mechanism of Action

Controlled pharmacological challenge studies in healthy volunteers establish which transmitter systems mediate which effects in humans, and largely confirm the transporter-based mechanism identified preclinically. Pretreatment with the serotonin uptake inhibitor citalopram attenuated most of MDMA's psychological effects and its cardiovascular effects; the 5-HT2 antagonist ketanserin reduced perceptual changes and emotional excitation while leaving positive mood largely intact; and the D2 antagonist haloperidol modestly reduced euphoria, indicating a secondary dopaminergic contribution [19, 72]. The selective norepinephrine transporter inhibitor reboxetine reduced MDMA-induced elevations in plasma norepinephrine, blood pressure, heart rate, subjective drug high, stimulation and emotional excitation, despite increasing plasma MDMA and MDA concentrations, demonstrating that transporter-mediated norepinephrine release is critical to the cardiovascular and stimulant-like effects [116]. The dual SERT/NET inhibitor duloxetine blocked serotonin and norepinephrine release by MDMA and MDA in cells expressing the human transporters and inhibited the corresponding physiological and subjective effects in vivo [117]. By contrast, clonidine, which inhibits vesicular norepinephrine release, did not inhibit the response to MDMA, confirming that release in humans is transporter-mediated rather than exocytotic [118]. Consistent with the in vitro inhibition data, MDMA's weak monoamine oxidase inhibition is unlikely to be pharmacologically relevant at the plasma concentrations achieved clinically [119].

Neuroendocrine and behavioural findings in humans support this profile but qualify some inferences drawn from animal work. MDMA increases plasma cortisol and prolactin, markers of serotonergic and noradrenergic activity, along with oxytocin, and enhances emotional empathy and prosocial behaviour [120]. However, MDMA-induced changes in emotional empathy were not related to plasma oxytocin concentrations in two independent studies [120, 121], so the causal role of oxytocin demonstrated in rodents has not been established in humans. Enantiomer-specific effects have likewise not matched preclinical predictions: in a randomized, double-blind crossover trial in 24 healthy participants, S-MDMA produced stronger stimulant-like subjective and cardiovascular effects and greater increases in prolactin, cortisol and oxytocin than R-MDMA, and R-MDMA did not produce more psychedelic-like effects, contrary to expectation from animal drug-discrimination studies [66]. Finally, whether the serotonergic neurotoxicity consistently observed in rodents occurs at clinical doses in humans remains unresolved; the available human data derive largely from retrospective studies of recreational polydrug users in whom dose, purity and frequency of exposure are unknown [72]. The pharmacokinetic consequences of MDMA's metabolism, including CYP2D6 autoinhibition and the acute pharmacodynamic tolerance observed with supplemental dosing, are discussed in Section 5.2.

5.2 Pharmacokinetics and Product Metabolism in Humans

The maximum proposed clinical dosing regimen historically studied consists of three divided single-dose exposures to racemic MDMA spaced approximately a month apart with an 80 mg or 120 mg initial dose followed by a 40 mg or 60 mg supplemental dose, administered 1.5 to 2 hours after initial dose at Cmax. Mean (%CV) Cmax and AUC at 125 mg MDMA HCl [122] is 223.5±38.5 ng/mL (N=136) and mean AUC: 948±172.9 ng*h/mL (N=136). The clinical dosing regimen does not reach steady state, as the intended usage is up to 3 exposures to single-dose with at least 2 weeks washout between doses.

Onset of MDMA effects occurs 30 to 60 minutes after oral administration of 75 to 125 mg [9, 10], peak effects appear 75 to 120 minutes post-drug [8, 11-13], and duration of effects lasts from 3 to 6 hours with most effects returning to baseline or near-baseline levels 6 hours after final drug administration [11, 12, 14]. Self-reported duration of effects may increase as the dose of MDMA increases [8]. In a repeated dose study, an initial dose of 50 mg MDMA HCl, followed two hours later by a second dose of 100 mg MDMA HCl, does not

significantly extend the duration of measurable physiological or subjective effects in comparison to a single dose of 100 mg MDMA HCl [102]. Orally administered MDMA has a half-life of 7 to 9 hours in humans and half-life is non-significantly extended from 10.41 hours to 10.48 hours if an additional dose is administered 2 hours after an initial dose [102]. MDMA and its metabolites have been found in oral fluid samples at much higher concentrations than in plasma, for 24 to 48 hours for the former and 12 to 47 hours for the latter after oral administration of 1 to 1.6 mg/kg MDMA HCl [123].

MDMA has not been studied in humans with intravenous administration. As such, absolute or relative bioavailability is unknown. At a dose of 75 mg, MDMA is rapidly absorbed in humans, with an observed Tmax of 1.8±0.4 hours by the oral route. At higher oral doses of 125 mg a slightly longer Tmax 2.4±1.0 hours was observed [15].

MDMA has been shown to be partially bound to plasma proteins in humans. The unbound fraction of MDMA in human plasma was measured to be 49% at therapeutically active concentration (200 ng/mL) [124]. The volume of distribution of MDMA at 1 mg/kg was observed to be 5.5±1.1 L/kg (dose range based on weight 43 mg-106 mg) in humans [125]. The volume of distribution of MDMA at 1.6 mg/kg was observed to be 5.5±1.3 L/kg (dose range based on weight 69 mg-150 mg) in humans [125].

MDMA metabolism in the liver is saturable in a dose-dependent manner and follows non-linear pharmacokinetics. MDMA is metabolized by N-demethylation to the only active metabolite MDA by several enzymes, including CYP2D6 (>30%), CYP1A2, CYP3A4, CYP2C19, and CYP2B6, followed by COMT. The parent compound and MDA are further O-demethylated to HHMA and HHA, respectively. Both HHMA and HHA are subsequently O-methylated mainly to HMMA and HMA. These four metabolites, particularly HMMA and HMA, are excreted in the urine as conjugated glucuronide or sulfate metabolites [126-131].

MDMA inhibits CYP2D6 function, which has been measured by examining the effects of MDMA on dextromethorphan metabolism. Inhibition of CYP2D6 by MDMA was demonstrated first in a physiological model derived from data collected after oral administration in humans [132]. O'Mathuna and colleagues present evidence that CYP2D6 activity may not fully recover until 10 days after MDMA [133, 134]. After reviewing their data and the literature on MDMA pharmacokinetics, de la Torre and colleagues concluded variation in CYP2D6 genotype is not clinically significant, due in part to the fact that the enzyme is inhibited in most people after administration of an active dose [101]. However, a pooled analysis of 10 clinical studies in healthy volunteers (n=194) examining predictor variables of physiological and psychological response to MDMA found a higher activity of the enzyme CYP2D6 predicted lower MDMA plasma concentrations, after adjusting for dose per body weight [135]. MDMA may produce increased activity of the enzyme CYP1A2, as evidenced by comparing caffeine metabolism before and after MDMA [136]. Findings support the enantioselective nonlinear metabolism of MDMA and its metabolites measured in blood and urine [137-139]. CYP2D6 may be involved in stereoselective metabolism of MDMA, but to a clinically insignificant degree [139].

Comparison of pharmacokinetic-pharmacodynamic relationships for MDMA reveals acute pharmacodynamic tolerance. Despite 7 to 9 hours of half-life of MDMA, and persistent high drug levels in the blood, most pharmacodynamic effects of the initial dose rapidly return to baseline within 4 to 6 hours [140]. A study comparing the effects of a single 100 mg dose with an initial administration of 50 mg followed 2 hours later by 100 mg, reported higher peak plasma MDMA than might be expected and lower levels of the MDMA metabolites HMMA and HMA, but other pharmacodynamic effects were not altered [102]. The initial dose appears to saturate or inhibit the metabolic pathway mediated by CYP2D6, leading a supplemental dose to

form metabolites at a lower rate than expected and increasing exposure to the parent drug. A study comparing the effects of a single 100 mg dose with an initial administration of 50 mg followed two hours later by 100 mg reported plasma MDMA concentrations increased by more than expected based on dose proportionality, Cmax+12.8% and AUC +16.2%. Inactive metabolite HMMA concentration decreasing in plasma by Cmax -38.2% and AUC -29.8%, which was more than what would be expected based on dose proportionality. These findings are further supported by examining plasma MDMA after two doses of 100 mg given four hours apart [141], plasma MDMA concentrations increased Cmax+23.1% and AUC +17.1%, and active metabolite MDA concentration increased in plasma by Cmax +14.2% and AUC +10.3%, which was also more than would be expected based on dose proportionality, likely due to metabolic autoinhibition of CYP2D6. These findings suggest that intensity of most subjective and physiological effects of MDMA would not be significantly impacted by the supplemental doses due to acute tolerance to its prototypical effects [141].

This acute tolerance could be caused by functional depletion of stored serotonin that prevent further release despite MDMA still being present [140], or are a result of MDMA transport into intracellular spaces is saturable due to limited transport capacity [142]. Additionally, reversible inhibition of tryptophan hydroxylase as observed in rodents [96], or internalization of serotonin reuptake transporters from the plasma membrane leading to less serotonin release [51], would support self-limiting effects of MDMA. On the other hand, although SERT can be internalized, the evidence suggests that accumulation of extracellular serotonin stimulated by MDMA affects SERT trafficking by perpetuating cell-surface SERT expression, but in contrast promotes internalization of DAT and NET [142, 143].

Although the hepatic route is thought to be the major route of metabolism in humans with 50% to 75% of the parent compound being metabolized, renal clearance accounts for 8% to 11% of elimination of MDMA and its metabolites. After 1.0 mg/kg MDMA HCl, the majority was excreted in urine as the inactive metabolites HMMA sulfate (13%), followed by DHMA 3-sulfate (9%), and HMMA glucuronide (5%), and only 8% as the parent compound MDMA [125]. After 1.6 mg/kg MDMA HCl, the majority was excreted in urine as the inactive metabolites HMMA sulfate (10%), followed by DHMA 3-sulfate (9%), and HMMA glucuronide (4%), and only 11% as the parent compound MDMA. Studies examining metabolism of 100 mg MDMA HCl reported similar excretion values [125, 144-148].

Metabolites are primarily excreted as glucuronide and sulfate conjugates [128, 149, 150] with some evidence for stereoselective metabolism of the glucuronide and sulfate metabolites [149]. Urinary excretion of the metabolite HHMA after 100 mg MDMA HCl in four men was 91.8±23.8 mol and 17.7% recovery [148]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [151]. Urinary recovery for MDMA and MDA were higher when a second dose of 100 mg MDMA HCl was administered 24 hours after an initial dose of 100 mg MDMA HCl when compared with a single dose [144]. 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 HCl [152].

Co-administration studies with MDMA after pre-treatment with CYP2D6 inhibiting prescription drugs paroxetine [153] and bupropion [154] have been completed. In addition, drug interaction studies with methylphenidate [140] and dextromethorphan [134] have been completed. MDMA reversibly inhibits CYP2D6 and decreases CYP3A4 activity, with CYP2D6 function normalizing after 10 days. MDMA increases CYP1A2 activity, as measured by caffeine challenge, by 20% to 40% when CYP2D6 is saturated or inhibited [134]. Due to known MDMA effects of CYP2D6 inhibition, drug interaction studies with CYP2D6 inhibitors are presented in detail below.

Paroxetine is an SSRI approved for PTSD and patients interested in MDMA-assisted therapy are likely to be on maintenance treatment with this drug. In a randomized, double-blind, crossover, placebo-controlled trial in healthy male volunteers who were CYP2D6 extensive metabolizers (N=7), paroxetine given for 3 days before MDMA resulted in significant increases of MDMA area under the plasma concentration-time curve from 0 to 27 hours (AUC27) by +23%, AUC from zero to infinity (AUC∞) by +27% and maximum plasma concentration (Cmax) by +17%, without significant differences in MDMA Tmax [153]. MDMA elimination-related pharmacokinetic parameters showed a significant reduction of plasma clearance by -29%, renal clearance by -19%, and hepatic clearance by -32%. Elimination half-life extended from 8.3 to 9.9 hours. A 21% decrease in Cmax of HHMA which is an MDMA metabolite, with no significant differences in AUC27, AUC∞, and elimination half-life were found. HMMA showed a decrease in plasma concentrations with a reduction in AUC27 of -28%, AUC∞ of -20% and Cmax of -46%. The active metabolite MDA, which is produced in the minor metabolic pathway, was shown to have an increase in Cmax of +17% and AUC27 +16%. Following paroxetine pretreatment, the urinary recovery (0-45 hours) of the parent compound MDMA increased by 11%; HHMA and HMMA urinary recoveries were 27% and 16% lower, respectively, compared to placebo. The ratio of Cmax values of paroxetine and its metabolite on Days 1 and 3 showed a threefold reduction, with no differences in Tmax. As these elevations were not clinically meaningful, drug interactions with previously approved PTSD medications that are also CYP2D6 inhibitors, such as paroxetine, would be suitable from a safety standpoint for co-administration with MDMA, although some subjective MDMA-induced effects may be reverted or attenuated [153].

As MDMA is a monoamine releaser that also weakly inhibits monoamine oxidase-A (see Section 4.3) [155], combining MDMA with an MAOI medication may present a risk of serotonin syndrome and increased sympathetic activity, as reported in four deaths associated with concomitant use of MDMA and the MAOI moclobemide [156]. MDMA's own MAO-A inhibition, however, is unlikely to be clinically relevant: an in vitro study reported IC50 values of MDMA and MDA for MAO-catalyzed deamination of serotonin (24.7 µM and >8.5 µM, respectively) and dopamine (19.2 µM and >8.4 µM, respectively), and concluded that the inhibitory potential (<20%) at plasma concentrations observed in humans (approximately 1 µM) was unlikely to be relevant [119].

Bupropion is a norepinephrine dopamine reuptake inhibitor approved for treatment of major depression and smoking cessation, and patients interested in MDMA-assisted therapy may be on maintenance treatment with this drug. Bupropion inhibits CYP2D6 and also competitively inhibits CYP2B6, which metabolizes bupropion to hydroxybupropion. 125 mg MDMA HCl was administered after 1 week of bupropion pre-treatment in a double-blind, placebo-controlled, crossover study in 16 healthy volunteers, in CYP2D6 extensive metabolizers (N=13) and intermediate metabolizers (N=3). Bupropion pretreatment increased the Cmax of MDMA by +14% ($p<0.01$), AUC24 by +33% ($p<0.001$), and prolonged its t1/2 by +24% ($p<0.01$). In contrast, bupropion pretreatment decreased the Cmax of MDA by -15% ($p<0.01$), and decreased AUC24 by - 12% but this failed to reach significance [154]. When results were re-analyzed with stereoselective methods [139], bupropion pre-treatment increased the Cmax of R-MDMA by +9% and the AUC from 0 to 24 hours (AUC24) by +25%. Bupropion pre-treatment increased the Cmax of S-MDMA by +16% and the AUC24 by +38%. In contrast, bupropion pre-treatment decreased the Cmax of R-MDA by -27% and the AUC24 by -26%, and the Cmax of S-MDA by -24% and the AUC24 by -20%. Bupropion pre-treatment decreased the Cmax and the AUC24 of CYP2D6- dependent inactive metabolite stereoisomers by approximately -40%. The changes that were observed in the intermediate metabolizers were comparable to the extensive metabolizers, although the intermediate metabolizer sample was small (N=3). Although changes in stereoselectivity based on CYP2D6 activity were observed, these are unlikely to have clinical relevance. Bupropion and hydroxybupropion

stereoisomer kinetics were unaltered by MDMA co-administration. As these elevations were not clinically concerning, drug interactions with non-serotonergic medications that are also CYP2D6 inhibitors, such as bupropion, would be suitable from a safety standpoint for co-administration with MDMA.

5.3 Safety and Efficacy

Overall, adverse effects of MDMA have been shown to be modest and generally have not been associated with serious discomfort in healthy volunteers or in subjects as observed in MAPS' Phase 2 or Phase 3 studies with PTSD and other indications. Risks posed by sympathomimetic effects of MDMA treatments were addressed by excluding people with pre-existing cardiovascular disease, cerebrovascular disease, or uncontrolled hypertension, and by monitoring blood pressure, body temperature, and pulse. Common reactions reported in clinical trials were transient and diminished as drug effects waned during the MDMA-assisted session and over the next 24 hours. Once the drug is fully cleared from the body within 48 hours post-dose, most reactions diminish within 3-4 days post-dose.

A clinical phase 3 trial conducted by Ot'alora et al. [157] also reported that MDMA-assisted psychotherapy is an efficacious treatment for PTSD. The randomized double-blind trial of 28 people with chronic PTSD also included the comparison of two active doses, i.e., 125 mg and 100 mg, with a low amount of 40 mg administered during 8-h psychotherapy sessions. Changes in the clinically administered PTSD scores one month after the two sessions of MDMA served as a primary outcome, and yearly follow-up assessments also occurred after the final dose. The results showed that the active group cohort significantly reduced the clinically administered PTSD scores with a mean score change of −26.3 with 125 mg, −24.4 with 100 mg, and −11.5 with 40 mg. However, statistical significance was reached only in the per-protocol set ($p = 0.03$). PTSD symptoms were well-controlled at the yearly follow-up assessment ($p < 0.001$), with 76% ($n = 25/28$) not meeting post-traumatic stress disorder criteria, and no side effects from the MDMA were observed.

In historical Phase 1 and Phase 2 studies, a subset of AEs were collected as spontaneously reported reactions in participants receiving a therapeutically active dose of MDMA: dry mouth, diarrhea, heavy legs, impaired judgment, and nystagmus. AEs that did not resolve within 7 days post-dose and were reported in 10% of participants in the active MDMA dose groups included: anxiety, fatigue, difficulty concentrating, increased irritability, insomnia, and low mood. The amount of placebo data in these studies precludes thorough separation of background events from reactions to MDMA.

A previous Phase 3 study showed the most common related treatment-emergent adverse events (TEAEs) reported more frequently in the MDMA group were muscle tightness (63.0% MDMA vs 11.4% placebo), decreased appetite (52.2% MDMA vs 11.4% placebo), nausea (30.4% MDMA vs 11.4% placebo), hyperhidrosis (19.6% MDMA vs 2.3% placebo), and feeling cold (19.6% MDMA vs 6.8% placebo). No serious adverse events (SAEs), adverse events of special interest (AESIs) suggestive of abuse potential, or AESIs involving cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias were reported in subjects who were randomized to the MDMA group in the Phase 3 study (n=46 of 90 treated). Three participants randomized to MDMA vs. five participants randomized to placebo reported AESIs of self-injurious behavior or suicidality.

Overall, the risks of SARs have been addressed and constrained by limited exposure and drug administration in controlled settings with adequate screening according to eligibility criteria defined in study protocols.

5.4 Clinical Trial Summaries

Shulgin and Nichols were the first to report on the effects of MDMA in humans [30]. In the 1970s, psychotherapists used MDMA-assisted therapy to treat psychological disorders including anxiety [32]. Legal therapeutic use of MDMA continued until its placement on the U.S. list of Schedule I drugs in 1985 [31, 35, 158]. An estimated 500,000 doses of MDMA were administered during therapy sessions in North America prior to its scheduling [28, 158]. A few uncontrolled human studies of MDMA occurred in the 1980s [159, 160] including Greer and Tolbert's study of MDMA in a psychotherapeutic context. Controlled human studies of MDMA commenced in the mid-1990s with a Phase 1 dose-response safety study [161, 162].

The first randomized placebo-controlled trial (RCT) of MDMA-assisted psychotherapy for PTSD was published in 2010 [163]. In a study of treatment-resistant patients, those who received two sessions of MDMA (plus an optional booster of 62.5 mg) had better outcomes than those who received a placebo. According to the study results, 83% of the patients given MDMA no longer met the criteria for PTSD, as opposed to only 25% of the patients in the placebo group [163]. The long-term follow-up results revealed that treatment effects persisted for three years [164].

Six randomized, double-blind, controlled clinical trials at five study sites were conducted from April 2004 to February 2017. Active doses of MDMA (75–125 mg, N=72) or placebo/control doses (0–40 mg, N=31) were administered to individuals with PTSD during manualized psychotherapy sessions in two or three 8-h sessions spaced a month apart. MDMA-assisted psychotherapy was efficacious and well tolerated in a large sample of adults with PTSD. These studies supported expansion into phase 3 trials and led to FDA granting Breakthrough Therapy designation for this promising treatment [165].

A search of clinicaltrials.gov was conducted in October 2026 looking for clinical trials utilizing MDMA as the intervention drug for the treatment of PTSD. Out of 125 clinical trials involving MDMA, 36 were completed with published results. From those studies, 9 were directed towards PTSD treatment. Other areas of interest for MDMA potential use included autism spectrum disorder, anxiety, substance-related disorders, major depressive and bipolar disorders, even the emotional effects of MDMA on startle response, cognition, and social interactions and in healthy adults.

Completed and published clinical trials of MDMA-assisted therapy for PTSD treatment, included Phase 2 and Phase 3 randomized, parallel, triple-blinded studies, as well as open label, single group studies. These trials were conducted by Multidisciplinary Association for Psychedelic Studies (MAPS) and enrolled a total of adult participants. All clinical trials with published results have been reported below (**Table 1**).

Table 1: Summary of completed investigational clinical trials with MDMA, and MDMA-assisted therapy in adult participants. Studies involving participants with PTSD highlighted in light grey.

Reference	Sponsor	Study Design	Objective	Enrollment	Populations	Dose
Searchfield et al; (2010) Int. J. Neurosci. [166]	Links Research and Grants	Randomized, double-blind, controlled, crossover (within-subjects) study	Investigate the short-term behavioral and neurophysiological effects of MDMA on tinnitus perception in adults with tinnitus	13	Adults with tinnitus	Oral dose of 30 mg MDMA or placebo in Cohort 1, n = 5, or 70 mg MDMA or placebo in Cohort 2, n = 8, with resting-state fMRI before and after dosing, administered in a controlled setting
Hysek et al; (2010) Emerg Med J. [167]	University Hospital, Basel, Switzerland	double-blind, placebo-controlled, crossover desgin	Investigate the interactive effects of the beta-blocker pindolol with MDMA on heart rate, blood pressure, body temperature, and adverse effects in healthy subjects.	16	Healthy adults	Oral dose of 1.6 mg/kg MDMA with 20 mg pindolol
Mithoefer et al; (2011) J Psychopharmacol. & Mithoefer et al; (2013) J Psychopharmacol. [163, 164]	Resilient Pharmaceuticals	Phase 2, randomized, double-blind, placebo-controlled study	Examine MDMA-assisted therapy in adults with PTSD whose symptoms had not improved after at least one prior treatment	20	Adults with chronic, treatment-resistant PTSD	Oral dose of 125 mg MDMA or placebo, optional supplemental dose of 62.5 mg MDMA or placebo 2 to 2.5 h after initial dose, administered during psychotherapy sessions
Hysek et al; (2011) Clin Pharmacol Ther. [116]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, crossover design with four experimental conditions	Asses the pharmacodynamic and pharmacokinetic effects of the interaction between the selective norepinephrine transporter inhibitor reboxetine and MDMA in healthy subjects	16	Health adults	Oral dose of 125 mg MDMA, 8 mg reboxetine, or placebo
Pardo-Lozano et al; (2012) PLoS One. [168]	Parc de Salut Mar	Open-label, signle arm	Evaluate the pharmacokinetics and physiological and subjective effects of MDMA considering gender and the genetic polymorphisms of CYP2D6, COMT, and 5-HTT	27	Healthy adults	Single oral dose of weight-adjusted MDMA at 1.4 mg/kg, range 75 to 100 mg
Hysek et al: (2012) Psychopharmacology (Berl). [169]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, 5-session, crossover design	Determine the autonomic effects of MDMA administered alone and after pretreatment with reboxetine, duloxetine, clonidine, carvedilol, and doxazosin, on pupillary function.	16	Healthy adults	Oral dose of 125 mg MDMA or placebo

Reference	Sponsor	Study Design	Objective	Enrollment	Populations	Dose
Hysek et al: (2012) PLoS One. [117]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, crossover design with four experiential conditions	Asses the effects of the serotonin and norepinephrine transporter inhibitor duloxetine, on the effects of MDMA in healthy subjects	16	Healthy adults	Oral dose of 125 mg MDMA, 120 mg duloxetine, or placebo
Oehen et al; (2013) J Psychopharmacol. [170]	Resilient Pharmaceuticals	Phase 2, randomized, double-blind, placebo-controlled study	Examine MDMA-assisted therapy in adults with PTSD whose symptoms had not improved after at least one prior treatment	12	Adults with chronic, treatment-resistant PTSD	Oral dose of 25 mg MDMA as low dose or 125 mg MDMA as full dose, supplemental dose of 12.5 mg for low dose or 62.5 mg for full dose, 3 experimental sessions interspersed with weekly non-drug psychotherapy sessions
Hysek et al; (2013) J Clin Psychopharmacol. [171]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, 4-session, crossover design	Determinate the effect of a pre-treatment with doxazosin, a alpha1-adrenergic receptor blocker, on the pharmacodynamics and pharmacokinetics of MDMA	16	Healthy male adults	Oral dose of 8 mg/d doxazosin, 125 mg MDMA, or placebo
Kirkpatrick et al; (2014) Neuropsychopharmacology. [172]	University of Chicago	Double-blind, crossover (within-subjects) study; single group	Investigate the acute effects of MDMA and oxytocin on social and emotional processing in healthy adults	65	Healthy adults aged 18–35 with previous MDMA use	Oral dose of 0.75 or 1.5 mg/kg MDMA, 20 or 40 IU intranasal oxytocin, or placebo, administered during psychotherapy sessions
Schmid et al; (2014) J Psychopharmacol. [173]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, crossover design with three experimental sessions	Investigate the acute effects of MDMA, methylphenidate, and placebo on social cognition tests	30	Health adults	Oral dose of 75 mg MDMA, 40 mg methylphenidate, and placebo
Hysek et al; (2014) Int J Neuropsychopharmacol. [140]	University Hospital, Basel, Switzerland	Randomized and counterbalanced, double-blind, placebo-controlled, cross-over study with four experimental test sessions	Compare the pharmacodynamic and pharmacokinetic effects of methylphenidate and MDMA administered alone or in combination in healthy subjects	16	Healthy colledge students	Oral dose of 125 mg MDMA, methylphenidate at 0.90 ± 0.1 mg/kg body weight, or placebo

Reference	Sponsor	Study Design	Objective	Enrollment	Populations	Dose
Papaseit et al; (2016) Neuropsychopharmacology. [174]	Parc de Salut Mar	Randomized, double-blind, crossover, and placebo-controlled	Evaluate the clinical pharmacology of mephedrone and its relative abuse liability compared with MDMA	12	Healthy male adults, who are recreational users of amphetamines, ecstasy, mephedrone, and cathinones with a lifetime exposure of at least six times	Oral dose of 200 mg mephedrone, 100 mg MDMA, and placebo
Boxler et al; (2017) J Proteome Res. [175]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled crossover study	Explore changes in endogenous plasma metabolites following a single intake of MDMA	15	Healthy adults	Single oral dose of 125 mg MDMA
Doss et al; (2018) Neuropsychopharmacology. [176]	University of Chicago	Randomized, double-blind, placebo-controlled study	Examine the effects of MDMA on emotional memory, separately during encoding and retrieval, in healthy adults	84	Healthy adults with previous MDMA use	Oral dose of 1.0 mg/kg MDMA, administered during psychotherapy sessions
Ot'alora et al; (2018) J Psychopharmacol. [177]	Resilient Pharmaceuticals	Phase 2, randomized, double-blind, dose-response study	Examine the safety and efficacy of MDMA-assisted therapy in adults with chronic, treatment-resistant PTSD	28	Adults with chronic, treatment-resistant PTSD	Oral dose of 100 or 125 mg MDMA as active dose or 40 mg MDMA as comparator, 2 blinded 8-hour experimental psychotherapy-assisted sessions spaced 1 month apart
Mithoefer et al; (2018) Lancet Psychiatry [178]	Resilient Pharmaceuticals	Phase 2, randomized, double-blind, placebo-controlled study	Compare the effects of low, medium and full doses of MDMA-assisted therapy in veterans and first responders with PTSD	26	Veterans and first responders with PTSD, many unresponsive to prior treatment	Oral dose of 30 mg MDMA as active control, 75 mg or 125 mg MDMA with psychotherapy, 30 mg and 75 mg groups then crossed over to 3 open-label sessions of 100 to 125 mg MDMA
Dodler et al; (2018) Psychopharmacology (Berl). [179]	University Hospital, Basel, Switzerland	Randomized, double-blind, cross-over, placebo-controlled	Investigate differences in the acute effects of equally cardiostimulant doses of MDMA, methylphenidate and modafinil compared directly within the same subjects.	24	Healthy adults	Oral dose of 125 mg MDMA, 60 mg methylphenidate, 600 mg modafinil, and placebo

Reference	Sponsor	Study Design	Objective	Enrollment	Populations	Dose
Danforth et al; (2019) Psychopharmacology (Berl) . [180]	Resilient Pharmaceuticals	Phase 2, single-site, randomized, double-blind, placebo-controlled study; exploratory	Explore the feasibility and safety of MDMA-assisted therapy for reducing the social fear and avoidance common in autistic adults	12	Autistic adults with severe social anxiety	Oral dose of 75 to 125 mg MDMA or inactive placebo, two 8-hour psychotherapy-assisted sessions in a controlled clinical setting
Monson et et al; (2020) Eur J Psychotraumatol. [181]	Resilient Pharmaceuticals	Phase 1/2, open-label, uncontrolled study; treatment development	Evaluate the safety and efficacy of cognitive-behavioral conjoint therapy (CBCT) combined with MDMA-assisted therapy in adults with chronic PTSD and their partners	12	Couples in which one partner has PTSD. Six couples with varying levels of baseline relationship satisfaction	Oral dose of 75 mg MDMA in session 1 and 100 mg MDMA in session 2 with psychotherapy, optional supplemental half-dose 1.5 h after initial dose in both sessions
Wolfson et al; (2020) Sci Rep . [182]	Resilient Pharmaceuticals	Phase 2, randomized, double-blind, placebo-controlled study; pilot	Explore the safety and efficacy of MDMA-assisted therapy in adults with anxiety associated with a life-threatening illness	18	Adults with anxiety related to a life-threatening illness	Oral dose of 125 mg MDMA HCl or placebo, optional supplemental dose of 62.5 mg MDMA HCl, administered during psychotherapy session
Mitchell et al; (2021) Nat Med. [183]	Resilient Pharmaceuticals	Phase 3, multi-site, randomized, double-blind, placebo-controlled study	Assess the safety and efficacy of MDMA-assisted therapy versus placebo with therapy in adults with severe PTSD	90	Adults with severe PTSD. Included common comorbidities such as dissociation, depression, history of alcohol and substance use disorders, and childhood trauma	Oral dose of 80 mg MDMA in session 1 and 120 mg MDMA in sessions 2 and 3 or placebo, supplemental half-dose of 40 mg or 60 mg 1.5 to 2.5 h after initial dose, 3 sessions each with psychotherapy
Christie et al; (2022) Front Psychiatry. [184]	Resilient Pharmaceuticals	Phase 2, multi-site, open-label study	Evaluate the safety and efficacy of MDMA-assisted therapy in adults with at least severe PTSD	32	Adults with PTSD with chronic pain	Oral dose of 80 or 120 mg MDMA, open-label, supplemental half-dose of 40 mg or 60 mg 1.5 to 2 h after initial dose, 3 sessions administered alongside psychotherapy
Atilia et al; (2022) Lancet Diabetes Endocrinol. [185]	University Hospital, Basel, Switzerland	Single-centre, case-control study with nested, randomised, double-blind, placebo-controlled crossover trial design	Use MDMA as a biochemical and psychoactive provocation test to investigate oxytocin deficiency in patients with arginine vasopressin deficiency (central diabetes insipidus)	30	Adults with arginine vasopressin deficiency (central diabetes insipidus) and healthy adults	Single oral dose of 100 mg MDMA or placebo

Reference	Sponsor	Study Design	Objective	Enrollment	Populations	Dose
Vizeli; (2022) Front Pharmacol. [186]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, two-period, crossover design	Test hypothesis that MDMA may facilitate fear extinction recall, which may be through the release of oxytocin	30	Healthy adult male participants	Single oral dose of 125 mg MDMA or placebo
Maples-Keller; (2022) J Psychopharmacol. [187]	Resilient Pharmaceuticals	Randomized placebo-controlled, two-group, parallel design	Investigated the effect of MDMA on fear learning, extinction training, and retention in healthy humans.	34	Healthy adults	Single oral dose of 100 mg MDMA or placebo
Mitchell et al; (2023) Nat Med. [188]	Resilient Pharmaceuticals	Phase 3, multi-site, randomized, double-blind study; confirmatory	Evaluate the safety and efficacy of MDMA-assisted therapy versus placebo with identical therapy in adults with moderate to severe PTSD	104	Adults with moderate to severe PTSD	Oral dose of 80 or 120 mg MDMA initially, supplemental half-dose of 40 mg or 60 mg 1.5 to 2 h after initial dose, administered during psychotherapy session
Straumann; (2023) Neuropsychopharmacology. [189]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, crossover design	Compare the co-administration of MDMA and LSD, with MDMA and LSD administration alone and placebo.	24	Health adults	Oral dose of 100 mg MDMA and 100 µg LSD together, 100 mg MDMA alone, 100 µg LSD alone, and placebo
Molla et al; (2023) Sci Rep. [190]	University of Chicago	Randomized, double-blind, placebo-controlled, crossover design	Examine the effects of MDMA on feelings of connectedness with an unfamiliar partner during a semi-structured casual conversation	18	Healthy adults with at least one instance of previous MDMA use	Oral dose of 100 mg MDMA or placebo
Molla et al; (2024) Imaging Neurosci (Camb). [191]	University of Chicago	Randomized, double-blind, crossover (within-subjects) study	Examine hemodynamic changes following MDMA versus placebo during gentle touch stimulation in healthy adults	22	Healthy adults with previous MDMA use	Oral dose of 1.5 mg/kg MDMA or placebo, administered in a controlled setting
Bershad et al; (2024) J Psychopharmacol. [192]	University of Chicago	Randomized, double-blind, placebo-controlled, crossover trial	Compare the effects of two doses of MDMA (0.75 mg/kg and 1.5 mg/kg) with placebo and methamphetamine (20 mg) in healthy adults	36	Healthy adults with previous MDMA use	Oral dose of 0.75 or 1.5 mg/kg MDMA, 20 mg methamphetamine, or placebo, administered in a controlled setting
Straumann et al; (2024) Neuropsychopharmacology. [66]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, crossover design	Compare the acute effects of S-MDMA, R-MDMA, and regular MDMA (a racemic mixture), and placebo in 24 healthy participants.	24	Health adults	Oral dose of 125 mg MDMA, 125 mg S-MDMA, 125 mg and 250 mg R-MDMA, and placebo

Reference	Sponsor	Study Design	Objective	Enrollment	Populations	Dose
Zhang et al; (2025) JAMA Netw Open. [193]	Stanford University	Randomized, double-blinded, within-participant, placebo- and baseline-controlled trial design	Determine whether baseline profiles of the negative affect circuit, measured in response to nonconscious (masked) threat stimuli, can distinguish subgroups with different acute responses to MDMA.	16	Healthy adults who had used MDMA on at least 2 prior occasions, but not in the past 6 months, and had subthreshold PTSD symptoms and early life trauma but no current psychiatric disorders.	Oral dose of placebo, 80 mg MDMA as low dose, and 120 mg MDMA as high dose across 1 placebo session and 2 MDMA sessions in randomized order, following 1 baseline session
Straumann et al; (2025) Neuropsychopharmacology. [194]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, crossover design with five experimental test sessions	Investigate responses to (i) placebo, (ii) MDMA, (iii) MDA, (iv) Lys-MDMA, and (v) Lys-MDA at equimolar doses	23	Healthy participants	Oral dose of placebo, 100 mg MDMA, 92 mg MDA, 172 mg Lys-MDMA, and 164 mg Lys-MDA at equimolar doses
Kachmarik et al; (2026) Front Neurosci. (Unpublished Parent Study: Stauffer et al; (2025) NCT05961527) [195, 196]	Portland VA Research Foundation, Inc	Exploratory pilot, open-label study	Embeded within Staufer et al. study (for preliminary research on MDMA assisted group therapy for PTSD) this sub-study examines within-person changes in inflammatory biomarkers.	23	Veterans with PTSD from both military sexual trauma, and combatt trauma.	Oral dose of 120 mg MDMA HCl initially, optional supplemental dose of 60 mg MDMA HCl 1.5 to 2 h after first dose
Arikci et al; (2026) Neuropsychopharmacology. [197]	University Hospital, Basel, Switzerland	Randomized, double-blind, placebo-controlled, crossover design	compared acute effects of 2C-B, MDMA, and psilocybin in 24 healthy participants	24	Healthy adults	Oral dose of 10, 20, and 30 mg 2C-B, 125 mg MDMA, and 25 mg psilocybin

5.5 Marketing Experience

The OPTI-MHCL is not marketed or approved for marketing in any regulatory jurisdiction. MDMA is currently scheduled drug product in Canada and may only be distributed through clinical trials, Health Canada's Special Access Program, and Subsection 56(1) exemption from the Controlled Drugs and Substances Act at this time. The OPTI-MHCL has not been submitted for investigational authorization, approval, registration or otherwise in any other countries.

At this time, OPTI-MHCL:

- Has been accepted for investigational authorization for two Clinical Trials in Israel

- Are being provided routinely into Australia to support the Authorized Prescriber Scheme for treatment of PTSD.

On 20 December 2019, U.S. Food and Drug Administration (FDA) has approved the treatment for Expanded Access, allowing certain patients access to the MDMA-assisted therapy for PTSD treatment before full market approval is granted. As of December 2023, a total of 2,051 research participants have been exposed to MDMA in clinical research studies globally. Qualitative and quantitative safety information has been consistent with the established safety profile as observed in clinical trials.

6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATORS

6.1 Summary

MDMA is a psychoactive compound that affects mood, perception, and increases prosocial feelings. Currently, MDMA is listed as a Schedule I controlled substance in Canada and is not permitted for medical use outside of approved research settings. Psychotherapists in the U.S. began to use MDMA as an adjunct to therapy in the mid to late 1970s, and narrative accounts describe therapeutic use with an estimated 500,000 doses of MDMA administered during therapy sessions in North America prior to its scheduling [28, 158]. These studies have demonstrated that MDMA can be safely administered to people with PTSD and other indications in a controlled clinical setting.

The pivotal Phase 3 trial [188] demonstrated that PTSD symptoms were significantly attenuated by MDMA-assisted therapy and confirm findings seen in Phase 2 studies. MDMA as an adjunct to supportive therapy was statistically superior for PTSD treatment in CAPS-5 severity scores from Baseline to 2 months after three blinded dosing sessions in comparison to therapy paired with an inactive placebo.

In comparison to anxiolytics, antidepressants, and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to therapy with rapid onset in some participants. A limited number of single divided-dose exposures to MDMA, spaced approximately 1 month apart in the therapeutically active dose range, are sufficient to obtain therapeutic outcomes. This intermittent dosing mitigates AE frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over medications that require daily dosing. Based on the current state of scientific knowledge and the risk/benefit profile of therapeutic doses of MDMA.

6.2 Administration

The final product will be packaged into labeled HPDE bottles. Management, handling, and administration of the investigational product will be completed in accordance with Canadian drug regulations, with access to the investigational product strictly limited to appropriate and defined study personnel.

Capsules should be swallowed whole with a full glass of water (240 ml), as per the study protocol. General administration should be followed as per the relevant clinical protocol. The participant will have preparation and rapport-building with the study staff prior to the initial dosing day and will be provided the opportunity to relax in a calm environment prior to each study visit. Adequate mental health support and counseling will be

available throughout the duration of the study. Participants will be monitored for at least 8 hours after administration of the drug product at each study visit.

6.3 Dosing

The current formulation consists of fixed doses in gelatin capsules of 40 and 60 mg MDMA HCl (as the hydrochloride salt) with the mannitol as the only excipient. There is a placebo to match. Due to a wide range of responses to identical mg/kg dosing between individuals, possibly as a result of inconsistent relationship between body weight and pharmacodynamic activity, previous human trials use initial doses between approximately 1 and 4 mg/kg MDMA (active doses range from 75 to 125 mg, with divided-dose 112.5mg to 187.5 mg, assuming a 70 kg individual,) to achieve a more consistent response between participants. Dose modifications are applicable, as per the study protocol.

In humans, onset of MDMA effects occurs approximately 30 to 60 minutes after initial administration, peak effects occur 75 to 120 minutes after administration and duration of effects lasts 3 to 6 hours [8, 9, 11, 12, 14]. A recent pharmacokinetics study investigated impacts of eating, or fasting on the uptake of MDMA, finding that a high-calorie, high-fat meal before oral administration does not alter plasma concentrations of MDMA, but did alter Tmax, concluding that MDMA can be administered without regard to food intake [198] Taking it with food may slightly delay the onset of subjective effects, but MDMA clinical sessions typically last several hours, thus this mild onset delay is unlikely to be clinically meaningful.

In a repeated dose study, an initial dose of 50 mg MDMA HCl, followed two hours later by a second dose of 100 mg MDMA HCl, does not significantly extend the duration of measurable physiological or subjective effects in comparison to a single dose of 100 mg MDMA HCl [102]. This is supported by additional pharmacokinetic data that demonstrated that split dosing compared to one dosing timepoint decreases plasma concentrations for the first four hours, but does not change overall exposure to MDMA, nor was there any change in subjective effects reported [198].

The pharmacokinetic properties of MDMA in humans have been characterized using initial oral doses up to 180 mg MDMA HCl. MDMA disposition in the body follows nonlinear pharmacokinetics. MDMA is metabolized in the liver by several enzymes. Recent pharmacokinetic work has confirmed MDMA inhibits CYP2D6, and that care should be taken when administering it with other CYP2D6 substrates [66, 198]. This autoinhibition may last for an extended period, with function normalizing up to 10 days post-MDMA. The enzymes CYP1A2, COMT, and MAO-A are also involved in the metabolism of MDMA. MDMA is metabolized by N-demethylation to MDA. The parent compound and its active metabolite MDA are further O-demethylated to HHMA and HHA, respectively. Both HHMA and HHA are subsequently O-methylated mainly to HMMA and HMA. These four metabolites, particularly HMMA and HMA, are known to be excreted in the urine as conjugated glucuronide or sulfate metabolites. The elimination half-life of active MDMA doses is 7 to 9 hours. The end of systemic exposure is within 48 hours post-dose [125].

Results from clinical studies to date suggest a favorable risk/benefit profile among PTSD participants treated with a two to three-session MDMA-assisted therapy, which also included follow-up non-drug therapy sessions. The largest Phase 2 and Phase 3 studies, sponsored by MAPS PBC (now Resilient Pharmaceuticals), used a split-dose regimen. In the first experimental session, participants received 80 mg MDMA HCl, followed by an optional supplemental 40 mg dose 1.5–2 hours later (up to 120 mg total). In the follow-up second and third experimental sessions, participants received either the same regimen or 120 mg followed by an optional 60

mg supplement (up to 180 mg total) [62, 63]. All other clinical trials for patients with PTSD have followed similar dosing schemes, all of them with split-dosing regimens, and operating between the 60-180 mg total dosing range.

6.4 Contraindications and Precautions

MDMA is contraindicated in patients with cardiovascular or cerebrovascular conditions where an acute increase in blood pressure may pose a significant clinical concern, such as aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels), arteriovenous malformation, or acute stroke or recent history of intracerebral hemorrhage and during or within 14 days following the administration of monoamine oxidase inhibitors (MAOI). The elevation of blood pressure and increased heart rate produced by MDMA, like that produced by other sympathomimetic drugs, can lead to increased risk in people with pre-existing medical conditions.

MDMA is a substrate of the serotonin, norepinephrine, and dopamine transporters and acts primarily as a releaser of these monoamines, with secondary reuptake inhibition (see Section 4.3). MDMA is a weak inhibitor of MAO-A in vitro; this effect is unlikely to be clinically relevant at therapeutic plasma concentrations [119], but because MDMA releases serotonin and norepinephrine, co-administration with MAOIs may cause serotonin syndrome and excessive sympathetic activation. MDMA has self-limiting subjective and physiological effects. SSRIs and SNRIs block MDMA's entry via the monoamine transporters and may eliminate or attenuate its effects.

Additional caution should be used for any patients who may take other CYP2D6 metabolized drugs, often drugs for mood disorders, cardiovascular conditions, or pain. Patients receiving such medications should be carefully evaluated, and potential drug-drug interactions should be considered when assessing eligibility and during treatment.

Enrollment in relevant studies with OPTI-MHCL must fulfill the particular eligibility criteria as per the clinical investigational plan for specific contraindicated medications and/or personal and intrafamilial psychological conditions. This includes monoamine oxidase inhibitors (MAOIs) as they can result in a potentially fatal serotonin syndrome and increases in sympathetic activity. Co-administration with serotonin and/or norepinephrine reuptake inhibitors (SSRIs/SNRIs) may eliminate or attenuate the effects of MDMA. Some of these drugs (e.g., paroxetine) also inhibit CYP2D6 and may increase MDMA exposure (see Section 5.2).

Upon discharge from the study setting, the patient should be delivered to the care of a responsible individual who can observe the patient for the remainder of 24 hours after the dose was administered.

6.5 Adverse Events

MDMA is responsible for a series of dose dependent physiological effects due to enhanced neurochemical release of serotonin, norepinephrine, and dopamine, and for indirect effects on hormone secretion, including oxytocin and AVP, which act on different target organs to modulate physiological functions in the body.

Overall, adverse effects of MDMA were modest and generally have not been associated with serious discomfort in healthy volunteers or in subjects in MAPS' Phase 2 or Phase 3 studies with PTSD and other indications. Risks posed by synergistic effects of MDMA and cardiovascular disease therapeutics were

addressed in those studies by excluding people with pre-existing cardiovascular disease, cerebrovascular disease or uncontrolled hypertension, and by monitoring blood pressure, body temperature, and pulse. Common reactions reported in clinical trials were transient and diminished as drug effects waned during the MDMA-assisted session and over the next 24 hours. Once the drug is fully cleared from the body within 48 hours post-dose, most reactions diminish within 3-4 days post-dose.

In historical Phase 1 and Phase 2 studies, a subset of AEs were collected as spontaneously reported reactions in participants receiving a therapeutically active dose of MDMA: anxiety, depressed mood, insomnia, obsessive rumination, restlessness, irritability, headache, disturbance in attention, dizziness, paresthesia, judgment impaired, hypersomnia, nausea, diarrhea, fatigue, asthenia, feeling cold, muscle tension, decreased appetite, hyperhidrosis, disturbed gait, dry mouth, thirst, sensation of heaviness, somnolence, and nystagmus. AEs that did not resolve within 7 days post-dose and were reported in 10% of participants in the active MDMA dose groups included: anxiety, fatigue, difficulty concentrating, increased irritability, insomnia, and low mood. MDMA is a sympathomimetic drug and transient dose-dependent increases in blood pressure and heart rate have been observed in Phase 2 and Phase 3 clinical trials that have not warranted medical treatment.

In a MAPS Phase 3 study, the most common related treatment-emergent adverse events (TEAEs) reported more frequently in the MDMA group were muscle tightness (63.0% MDMA vs 11.4% placebo), decreased appetite (52.2% MDMA vs 11.4% placebo), nausea (30.4% MDMA vs 11.4% placebo), hyperhidrosis (19.6% MDMA vs 2.3% placebo), and feeling cold (19.6% MDMA vs 6.8% placebo). No SAEs, AESIs suggestive of abuse potential, or AESIs involving cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias were reported in subjects who were randomized to the MDMA group in the Phase 3 study (n=46 of 90 treated). Three participants randomized to MDMA vs. five participants randomized to placebo reported AESIs of self-injurious behavior or suicidality.

Common anxiety-related psychiatric symptoms were reported equally in both the MDMA and placebo arms in the Phase 3 trial [183]. As of December 2023, there have been 19 event-level SAEs in 14 participants in the clinical development program following MDMA administration across indications. Of these, 18 were considered unrelated and one was determined to be a SAR (increased ventricular extrasystoles), reported in Phase 2 clinical trial [178]. Overall, the risks of SARs have been addressed and constrained by limited exposure and drug administration in controlled settings with adequate screening according to eligibility criteria defined in study protocols.

Safety findings are summarized based on the review of the pooled data of MDMA trials investigating MDMA globally over the past four decades (**Table 2**).

Table 2: Safety findings related to orally administered MDMA.

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
Arikci et al. (2026)	24	Doses of 10, 20, and 30 mg 2C-B, 125 mg MDMA, and 25 mg psilocybin	"2C-B dose-dependently but only mildly increased blood pressure, with 30 mg 2C-B inducing significantly lower increases compared with MDMA and psilocybin ($p < 0.001$). Psilocybin and MDMA induced comparable increases in blood pressure. Only 30 mg 2C-B and not the lower doses increased heart rate compared with placebo ($p < 0.01$), and these increases were similar to psilocybin but lower than MDMA ($p < 0.001$). Overall, MDMA induced the highest

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
			cardiovascular stimulation, followed by psilocybin and 2C-B, reflected by the rate pressure products. Psilocybin ($p < 0.001$) and 20 and 30 mg 2C-B (both $p < 0.05$) but not MDMA increased body temperature compared with placebo. None of the drugs had an effect on QT-time. All conditions, except 10 mg 2C-B, increased the total acute (0-9 h) adverse effect score on the List of Complaints compared with placebo (all $p < 0.001$). No severe adverse events were observed." [197]
Straumann et al. (2025)	23	Dose of placebo, 100 mg MDMA, 92 mg MDA, 172 mg Lys-MDMA, and 164 mg Lys-MDA at equimolar doses	"MDMA, MDA, and Lys-MDA produced comparable increases in blood pressure, heart rate, body temperature, and pupil diameter. However, effects of MDA and Lys-MDA were longer-lasting compared with MDMA. MDA produced marginally greater pupil dilation following light exposure than MDMA (Supplementary Fig. S6). Lys-MDMA did not produce any changes in blood pressure, heart rate, body temperature, or pupil size. MDA and Lys-MDA produced significantly more acute and subacute adverse effects on the List of Complaints compared with MDMA. More subacute adverse effects after MDA and Lys-MDA were also reported by female participants compared to male participants and by participants who were genetically determined poor metabolizers (PMs) of CYP2D6 compared to intermediate (IMs) and extensive metabolizers (EMs)." [194]
Zhang et al. (2025)	16	Dose of placebo, 80 mg MDMA as low dose, and 120 mg MDMA as high dose across 1 placebo session and 2 MDMA sessions in randomized order, following 1 baseline session	No AEs of concern reported, no interventions required. No SAEs reported. [193]
Molla et al. (2024)	22	Dose of 1.5 mg/kg MDMA or placebo, administered in a controlled setting	No AEs of concern reported, no interventions required. No SAEs reported. [191]
Bershad et al. (2024)	36	Dose of 0.75 or 1.5 mg/kg MDMA, 20 mg methamphetamine, or placebo, administered in a controlled setting	"Both doses of MDMA and MA significantly increased heart rate [$F(3,105) = 11.33$, $p < 0.001$] and MAP [$F(3,105) = 13.87$, $p < 0.001$], compared to placebo." [192]
Straumann et al. (2024)	24	Dose of 125 mg MDMA, 125 mg S-MDMA, 125 mg and 250 mg R-MDMA, and placebo	"All substances produced similar acute and subacute adverse effects on the List of Complaints. Frequently reported adverse effects included fatigue, headache, decreased appetite, feeling dull, lack of concentration, and dry mouth. All substances nominally increased self-ratings of depressive mood on the BDI 1–3 days after substance administration. Significantly higher ratings were seen for S-MDMA compared with placebo, with no significant differences between

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
			active drug substances. No severe adverse events were observed." [66]
Straumann et al. (2023)	24	Dose of 100 mg MDMA and 100 µg LSD together, 100 mg MDMA alone, 100 µg LSD alone, and placebo	"MDMA and the LSD + MDMA combination induced higher increases in blood pressure, heart rate, and pupil size compared with LSD alone. Body temperature increased similarly for LSD and the LSD + MDMA combination but less when MDMA was administered aloneThe LSD + MDMA combination and LSD alone produced similar total acute and subacute adverse effects scores on the List of Complaints, exceeding those of MDMA. Frequently reported adverse effects on the List of Complaints are presented in Supplementary Table S6. Headache, lack of energy, loss of appetite, and dry mouth were similarly often reported with MDMA, LSD, and LSD + MDMA. Acute nausea was more frequent with MDMA than LSD. No severe adverse events were observed." [189]
Molla et al. (2023)	18	Dose of 100 mg MDMA or placebo	No AEs of concern reported, no interventions required. No SAEs reported. [190]
Mitchell et al. (2023)	104	Session 1: initial dose of 80 mg MDMA HCl followed by additional 40 mg MDMA HCl 1.5 to 2 hours later. Sessions 2 and 3: initial doses of 80 mg or 120 mg MDMA HCl followed by additional 40 mg or 60 mg MDMA HCl 1.5 to 2 hours later.	Most participants (102/104, 98.1%) experienced at least one treatment-emergent adverse event (TEAE) during the study; seven experienced a severe TEAE (MDMA-AT, n = 5 (9.4%); placebo with therapy, n = 2 (3.9%)). None had a serious TEAE. Two participants (3.9%) in the placebo with therapy group discontinued treatment due to TEAEs. Frequently reported TEAEs (occurring with incidence >10% and at least twice the prevalence in the MDMA-AT group versus the placebo with therapy group) included muscle tightness, nausea, decreased appetite and hyperhidrosis. These were mostly transient and of mild or moderate severity. Eight participants (MDMA-AT, n = 7; placebo with therapy, n = 1) experienced cardiac TEAEs, which included palpitations and tachycardia; all were mild. Nine participants (MDMA-AT, n = 7; placebo with therapy, n = 2) experienced vascular TEAEs; all were mild, except for one participant in the MDMA-AT group who had a history of hypertension, who was not taking anti-hypertensive medications and who experienced a TEAE of moderate hypertension. Participants in the MDMA-AT group experienced temporary dose-dependent increases in mean blood pressure (BP) and pulse during experimental sessions compared to the placebo with therapy group. Psychiatric TEAEs occurred at a similarly high frequency in both groups (MDMA-AT, n = 44 (83.0%); placebo with therapy, n = 37 (72.5%)), with suicidal ideation, insomnia and anxiety reported most frequently. Psychiatric TEAEs were mostly mild to moderate; three severe events occurred in the MDMA-AT group (5.7%; n = 1 each: dissociation, flashback, and grief reaction) and two in the placebo with therapy group (3.9%; n = 1 each: agitation and anxiety). No severe TEAEs of suicidal ideation or behavior were reported. [188]
Vizeli, P., et al. (2022)	15	125 mg	No AEs of concern reported; no intervention required. No SAEs reported. [186]
Maples-Keller, J.L., et al. (2022)	17	100 mg	There were no cardiovascular AEs and no participants withdrew due to harms. The most common AEs were elevated blood pressure, headache, anxiety, and tachycardia. All adverse events ranged from mild to moderate severity and were transient in nature and did not require medication or intervention. There were no serious adverse events reported. [187]

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
Kloft, L., et al. (2022)	61	75 mg	No AEs of concern reported, no interventions required. No SAEs reported. [199]
Mitchell et al. (2021)	46	Session 1: initial dose of 80 mg MDMA HCl followed by additional 40 mg MDMA HCl 1.5 to 2 hours later. Sessions 2 and 3: initial doses of 80 mg or 120 mg MDMA HCl followed by additional 40 mg or 60 mg MDMA HCl 1.5 to 2 hours later.	TEAEs were typically transient, mild to moderate in severity, and included muscle tightness, decreased appetite, nausea, hyperhidrosis and feeling cold. No increase in adverse events related to suicidality was observed in the MDMA group. A transient increase in vital signs (systolic and diastolic blood pressure and heart rate) was observed in the MDMA group. Two participants in the MDMA group had a transient increase in body temperature. Two participants in placebo group, reported three SAEs during the trial, two SAEs of suicidal behavior reported by the same participant and one SAE of suicidal ideation that led to self-hospitalization. Five participants in the placebo group and three participants in the MDMA group reported AESIs of suicidal ideation, suicidal behavior or self-harm in the context of suicidal ideation. One participant in the placebo group reported two cardiovascular AESIs in which underlying cardiac etiology could not be ruled out. One participant in MDMA group, who met the criterion as a non-responder, discontinued participation due to being triggered by the CAPS-5 assessments and to an adverse event of depressed mood following an experimental session.[183]
Wang et al. (2021)	33	Session 1: initial dose of 80 mg MDMA HCl followed by additional 40 mg MDMA HCl 1.5 to 2 hours later. Sessions 2 and 3: initial doses of 80 mg or 120 mg MDMA HCl followed by additional 40 mg or 60 mg MDMA HCl 1.5 to 2 hours later.	Frequently reported AEs on the day of experimental sessions included muscle tightness, headache, insomnia, nystagmus, and nausea, that were rated as either mild or moderate. One participant withdrew from the study due to an AE of increased nightmares which was reported as mild. Five participants experienced an SAE posttreatment; however, these AEs did not occur on the day of experimental sessions or 2 days after. All five SAEs (syncope, headache, anal fissure, exacerbation of suicidal ideation, and suicide attempt) occurred between 5 and 78 days post experimental session. There was one serious SAE of an aborted suicide attempt in a participant 28 days after their third experimental session, which was resolved by the next day. The participant had a lifetime history of ongoing suicidal ideation and two previous suicide attempts. The study investigator determined that this particular SAE was unrelated to treatment given that it occurred nearly a month after the last MDMA session. At study termination, five participants reported the presence of suicidal ideation, of whom four had a history of suicidal ideation; no participants reported serious suicidal ideation or suicidal behavior. [200]
Searchfield, G.D., et al. (2020)	13	Study 1: 30 mg (~0.42 mg/kg) Study 2: 70 mg (~1 mg/kg)	No AEs of concern reported, no interventions required. No SAEs reported. [166]
Holze, F., et al (2020)	28	125 mg (~1.8 mg/kg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [201]
Wolfson, P.E., et al. (2020)	18	125 mg (followed by optional half dose)	Most TEAEs were likely associated with participants' life-threatening illnesses. Psychiatric adverse events were infrequent, and MDMA was not associated with serious suicidal ideation or behavior. [182]
Sessa, B., et al. (2019 & 2021)	14	125 mg (~1.8 mg/kg)	No AEs of concern, no interventions required. No SAEs reported. [202, 203]

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
Bershad, A.K., et al. (2019 & 2020)	36	0.75 mg/kg 1.5 mg/kg	No AEs of concern were reported, and no interventions required. No SAES were reported. [204, 205]
Wagner et al. (2019)	12	Session 1: 75 mg + optional half dose Session 2: 75/ 100 mg + optional half dose	No AEs of concern were reported, and no interventions required. No SAES were reported. [206]
Mithoefer et al. (2018)	26	30 mg, 75 mg, or 125 mg (followed 1.5-2.5 h later by optional half dose) Followed by optional open-label 100 mg or 125 mg MDMA HCl, (followed 1.5-2.5 h later by optional half dose)	85 adverse events were reported by 20 participants during the study, of which four (5%) occurred before drug administration. Four (5%) of 85 were serious adverse events: three were deemed unrelated and one possibly related to study drug treatment. Serious adverse events deemed unrelated were suicidal ideation in response to life events, major depression (same participant), and appendicitis. One participant who had exhibited increased ventricular extrasystoles during the third open-label session, had an overnight hospital stay and recovered fully without evidence for vascular or structural cardiac disease. The most frequently reported treatment-emergent adverse events were psychiatric symptoms, and the most frequently reported expected adverse reactions during experimental sessions included anxiety, headache, fatigue, and muscle tension. Most adverse reactions were mild to moderate in severity, with occurrence decreasing across the 7 days following experimental sessions. [178]
Ot'alora et al. (2018)	28	40 mg, 100 mg, or 125 mg Followed 1.5-2.5 h later by optional half dose in two blinded sessions, followed by third open-label session with the same dose.	There were no drug-related serious adverse events, and the treatment was well-tolerated. During the blinded segment, at least one TEAE was reported by 1/6 (40 mg), 5/9 (100 mg,) and 9/13 (125 mg) participants. TEAEs were reported more frequently in both active dose groups (100 mg, 42.1% of 38 adverse events (AEs) during this period; 125 mg, 52.6%) compared to the 40 mg group (5.3%). Most psychiatric TEAEs occurred in active dose groups, including anxiety (33.3% of 100 mg, 30.8% of 125 mg participants), depressed mood (22.2% of 100 mg, 15.4% of 125 mg participants), and irritability (22.2% of 100, 7.7% of 125 mg participants). Fifteen TEAEs were reported during the open label segment and were also mostly psychiatric including anxiety and obsessive rumination, each occurring in 3.8% of participants, and suicidal ideation, occurring in 7.7% of participants. [177]
Danforth, A.L., et al. (2018)	12	75 mg (100 mg second dose), or 100 mg (125 mg second dose)	There were no serious adverse psychological or medically related health events. Although moderate elevations in blood pressure, heart rate, and temperature were observed during most experimental sessions, no participants encountered any acute cardiovascular or hyperthermia crises. [180]
Gabay, A.S., et al. (2018 & 2019)	20	100 mg (~1.4 mg/kg)	No AEs of concern, no interventions required. No SAEs reported. [207, 208]
Carhart-Harris, R.L., et al. (2014 & 2015)	25	100 mg (~1.4 mg/kg)	No AEs of concern, no interventions required. No SAEs reported. [23, 209, 210]
Schmidt, A., et al. (2017 & 2018)	24	125 mg (~1.8 mg/kg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [211, 212]

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
Steuer, A.E., et al. (2015) & Boxler, M.I., et al. (2018)	16	125 mg (~1.8 mg/kg)	Bupropion did not alter adverse effects of MDMA No AEs of concern were reported, no intervention required. No SAEs reported. [149, 150, 213]
Hysek, C.M., et al. (2014) & Boxler, M.I., et al. (2017)	16	125 mg (~1.8 mg/kg)	Concomitant methylphenidate does not enhance the risk of MDMA-induced increase in body temperature. No AEs of concern reported, and no interventions needed. No SAEs reported. [140, 175]
Hysek, C.M., et al. (2013)	16	125 mg (~1.8 mg/kg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [171]
Schmidt, A., et al. (2014)	30	75 mg (~1.1 mg/kg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [173]
Oehen et al. (2013)	14	25 mg or 125 mg (followed 1.5-2.5 h later by optional half dose)	No drug-related serious adverse events occurred, and no medical intervention was required during or following the MDMA sessions. [170]
Hysek, C.M., et al. (2012)	16	125 mg (~1.8 mg/kg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [117]
Mithoefer et al. (2011)	22	125 mg followed 1.5-2.5 h later by optional 53 mg	There were no drug-related serious adverse events, no evidence of impaired cognitive function as measured by neuropsychological testing, and no adverse neurocognitive effects or clinically significant blood pressure increases. [163]
Hysek, C.M., et al. (2011)	16	125 mg (~1.8 mg/kg)	No AEs of concern reported, no and no interventions required. No SAEs reported. [116]
Bosker, W.M., et al. (2010 & 2012)	16	25 mg (~0.36 mg/kg), 50 mg (~0.7 mg/kg) or 100 mg (~1.4 g/kg)	Sleep deprivation worsened driving skills (signs of weaving); no dose of skills (signs of weaving); no dose of MDMA mitigated, or worsened, performance. No AEs of concern were reported, and no interventions required. No SAEs reported. [214, 215]
Kuypers, K.P., et al. (2006 & 2007)	18	75 mg (~1.1 mg/kg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [111, 216]
Kuypers, K.P. and J.G. Ramaekers (2006 & 2007)	18	75 mg (~1.1 mg/kg), 100 mg (~1.4 mg/kg)	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [109, 110]
Kuypers, K.P., et al. (2007, 2008)	14	50 mg (~0.7 mg/kg) followed 3 h later by 75 mg (~1.1 mg/kg)	No AEs of concern reported, and no interventions required. No SAEs reported. [217, 218]
Lamers, C.T., et al. (2003)	12	75 mg (~1.1 mg/kg)	No AEs of concern reported, and no interventions required. No SAEs reported. [219]
de Sousa Fernandes Perna, E.B., et al. (2014)	15	75 mg (~1.1 mg/kg)	No AEs of concern reported, and no interventions required. No SAEs reported. [220]
Yubero-Lahoz, S., et al. (2015)	18	75 mg (~1.1 mg/kg)	No AEs of concern, and no interventions needed. No SAEs reported. [221]
Bedi, G., et al. (2014 & 2010)	21	0.75 mg/kg; 1.5 mg/kg	No AEs of concern were reported, and no interventions required. No SAEs reported. [24, 57]
Baggott, M.J., et al. (2016)	12	1.5 mg/kg	No AEs of concern reported, no interventions required. No SAEs reported. [222]
Frye, C.G., et al. (2014) & Clark, C.M., et al. (2015)	36	0.75 mg/kg; 1.5 mg/kg	No AEs of concern were reported, and no interventions required. No SAEs reported. [223, 224] Sponsor conducted post-hoc analysis of 2-lead ECG and found low likelihood of QT prolongation

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
Kirkpatrick, M.G. and H. de Wit (2015)	33	0.5 mg/kg; 1.0 mg/kg (max to 125 mg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [225]
Bershad, A.K., et al. (2017)	26	0.5 mg/kg; 1.0 mg/kg	No AEs of concern were reported, and no interventions required. No SAEs were reported. [226]
Doss, M.K., et al. (2018)	40	1.0 mg/kg	No AEs of concern reported, and no interventions required. No SAEs reported. [176]
Wardle, M.C. and H. de Wit (2014)	36	0.75 mg/kg; 1.5 mg/kg	MDMA increased desire to take drug again over placebo control. No interventions were needed. No SAEs occurred. [26]
Bouso, J.C., et al. (2008)	4	50 mg, 75 mg	No AEs of concern reported, and no interventions required. No SAEs reported. [55]
Papaseit, E., et al. (2016)	12	100 mg (~1.4 mg/kg)	No AEs of concern reported, and no intervention required. No SAEs reported.[174]
Peiro, A.M., et al. (2013)	10	100 mg (~1.4 mg/kg), 50 mg+100 mg 2 h later	No AEs of concern reported, and no interventions required. No SAEs reported. [102]
Pardo-Lozano, R., et al. (2012)	27	1.4 mg/kg (75-100 mg)	No AEs of concern reported, and no interventions required. No SAEs reported. [168]
Yubero-Lahoz, S., et al. (2012)	21	1.5 mg/kg (75-100 mg)	No AEs of concern were reported, nor interventions required. No SAEs were reported. [136]
Yubero-Lahoz, S., et al. (2011)	12	100 mg (~1.4 mg/kg)	No AEs of concern, and no interventions needed. No SAEs reported. [134]
Farre, M., et al. (2004)	10	100 mg day 1+100 mg day 2 (~1.4 mg/kg per day)	Diagnostic criteria of isolated systolic hypertension (>140 mmHg) were met by 6 subjects following the first dose of MDMA and 8 subjects following the second dose; mean duration of 1 h (range 0.5-2) following the first dose and 1.4 h (range 0.5-3) following the second dose. Two subjects met diagnostic criteria of sinus tachycardia (>100 beats/minute), both following the second dose of MDMA. Tachycardia lasted between 15 and 30 minutes. No intervention required and no SAEs reported. [144]
Pacifici, R., et al. (2001 & 2002)	27	100 mg (~1.4 mg/kg), second dose 100 mg (administered 4 hours vs. 24 hours post first dose)	MDMA produced time-dependent decrease in CD4/CD8 T-cell ratio due to a decrease in the number of CD4 T-helper cells, decrease in functional responsiveness of lymphocytes to mitogenic stimulation, and a simultaneous increase in natural killer cells. Second dose either 4 or 24 hours later accentuated the findings. No SAEs were reported. [227, 228]
de la Torre, R., et al. (2005)	10	100 mg day 1+100 mg day 2 (~1.4 mg/kg per day)	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [229]
Pacifici, R., et al. (2001) & Hernandez-Lopez, C., et al. (2002)	9	100 mg (~1.4 mg/kg) MDMA + ethanol (0.8 g/kg)	No AEs of concern, and no interventions required. No SAEs reported. [230, 231]
Cami, J., et al. (2000) Mas, M., et al. (1999)	14	50 mg (~0.7 mg/kg) 75 mg (~1.1 mg/kg) 125 mg	No AEs of concern reported, and no interventions required. No SAEs reported. [9, 10, 15]

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
de la Torre, R., et al. (2000)		(~1.8 mg/kg) 150 mg (~2.1 mg/kg)	
O'Mathuna, B., et al. (2008)	15	1.5 mg/kg (followed by dextromethorphan)	No AEs of concern reported, and no interventions required. No SAEs reported. [133]
Tancer, M. and C.E. Johanson (2003)	12	1 mg/kg	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [13]
Freedman, R.R., C.E. Johanson, and M.E. Tancer (2005)	10	2 mg/kg	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [232]
Johanson, C.E., et al. (2006)	8	1 mg/kg, 1.5 mg/kg	No AEs of concern were reported, and no interventions required. No SAEs were reported. [233]
Tancer, M.E. and C.E. Johanson (2001)	15	1.1 mg/kg, 1.6 mg/kg, 2.1 mg/kg	No AEs of concern were reported, and no interventions required. No SAEs were reported. [234]
Tancer, M.E. and C.E. Johanson (2007)	7	2 mg/kg	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [235]
Dumont, G.J., et al. (2009 & 2010), Lansbergen, M.M., et al. (2011)	16	100 mg (~1.4 mg/kg)	One subject reported "feeling unwell" under the influence of MDMA condition. No other AEs of concern reported, and no interventions required. No SAEs were reported. [58, 236-238]
Samyn, N., et al. (2002)	12	75 mg (~1.1 mg/kg)	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [239]
Kirkpatrick, M.G., et al. (2012), Marrone, G.F., et al. (2010)	11	100 mg (~1.4 mg/kg)	No AEs of concern were reported, and no interventions were required. No SAEs were reported. [240, 241]
Veldstra, J.L., et al. (2012)	19	100 mg (~1.4 mg/kg)	MDMA showed no significant effects on driving compared with placebo. No AEs of concern were reported, and no interventions were required. No SAEs were reported. [242]
Parrott, A.C., et al. (2011), Stough, C., et al. (2012)	61	100 mg (~1.4 mg/kg)	Driving under the influence of MDMA was worse than after both methamphetamine and placebo. No AEs of concern were reported, and no interventions were required. No SAEs were reported. [243-245]
Baggott, M.J., et al. (2008), Baggott, M.J., et al. (2016)	28	Study 1: 1.5 mg/kg, with / without prazosin Study 2: 1.5 mg/kg, followed 30 minutes by 20 ml/kg water	Study 1: No AEs of concern reported, no intervention required. No SAEs reported. Study 2: MDMA acutely exaggerates the hyponatremic effects of water. No AEs of concern reported, and no interventions required. No SAEs reported. [246, 247]
Desrosiers, N.A., et al. (2013), Abraham, T.T., et al. (2009), Hartman, R.L., et al. (2014)	50	1.0 mg/kg, 1.6 mg/kg (maximum 150 mg)	Significantly lower plasma HMMA AUC0-3h in African American participants after the low dose. The same was found for females. No AEs of concern were reported, and no interventions were required. No SAEs reported. [123, 152, 248]

Authors & Year	Enrollment in Study	Dose of MDMA HCl	Safety Outcomes
Kolbrich, E.A., et al. (2008), Mueller, M., et al. (2009)	9	1.0 mg/kg, 1.6 mg/kg (maximum 150 mg)	No AEs of concern were reported, and no interventions required. No SAEs reported. [95, 125]
Harris, D.S., et al. (2002)	8	0.5 mg/kg; 1.5 mg/kg	No AEs of concern reported, and no interventions required. No SAEs reported. [11]
Hasler, F., et al. (2009)	15	1.6 mg/kg	No information on AEs reported; no SAEs reported. [249]
Gamma, A., et al. (2000), Frei, E., et al. (2001)	16	1.7 mg/kg	No AEs of concern reported, no intervention required. No SAEs reported. [250, 251]
Liechti, M.E., et al. (2000)	14	1.5 mg/kg	No AEs of concern reported, no intervention required. No SAEs reported. [252]
Liechti, M.E. and F.X. Vollenweider (2000)	13	1.5 mg/kg	No AEs of concern reported, no intervention required. No SAEs reported. [253]
Vollenweider, F.X., et al. (1998 & 1999)	16	1.7 mg/kg	One individual showed increased BP of 240/145 SBP/DBP, resolved with no medical intervention needed. Changes in BP significant for SBP, not for DBP but present. [14, 254]
Helmlin, H.J., et al. (1996), Lanz, M., et al. (1997)	2	1.7 mg/kg 1.5 mg/kg	No information on AEs of concern reported; no SAEs reported. [128, 129]
Grob, C.S., et al. (1996), Grob, C.S., et al. (1998), Chang, L., et al. (2000)	18	0.25 mg/kg to 2.5 mg/kg in 0.25 mg/kg increments; each person received 2 ascending doses	No AEs of concern were reported, and no interventions required. No SAEs were reported. [161, 162, 255]
Greer, G. and R. Tolbert (1986)	29	75-150 mg (~1.1 - 2.1 mg/kg), 200 mg (~2.9 mg/kg) half-dose offered later	No AEs of concern reported, and no interventions required. No SAEs reported. [160]
Downing, J. (1986)	21	Varied, self-selected, 0.8 mg/lb, average 1.14 mg/lb (app. 2.5 mg/kg)	No AEs of concern reported, no interventions required. No SAEs reported. [159]
Jardim, A.V., et al. (2020)	3	75 mg (~1.1 mg/kg) or 125 mg (~1.8 mg/kg) with half-dose offered later	No AEs of concern reported. No SAEs reported. [256]

6.6 Pregnancy

Human data on effects of MDMA during pregnancy is limited. Several epidemiological survey studies have attempted to study this issue and found mixed results [257-259]. A 2012 survey of 96 women in the UK interviewed about their drug use during pregnancy found a link between self-reported extent of prenatal Ecstasy exposure and delays in infant development at 12 months, with heavily exposed infants delayed in mental and motor development, but not language or emotional development [260]. These results were repeated in a 2016 survey of 96 mothers who reported heavier Ecstasy use (1.3±1.4 tablets per week) during pregnancy. Infants had motor delays from 4 months to 2 years of age that were not attributable to other drug or lifestyle factors [261]. There is no suspicion of human teratogenicity or data that supports genotoxic potential, and non-clinical reproductive toxicity studies of relevance for early human pregnancy have been completed and demonstrated results that do not generate strong suspicion of human teratogenicity/fetotoxicity.

6.7 Abuse and Overdose Potential

A study was conducted with 22 individuals (mean age 23.6) with a history of stimulant drug use (more than six times) and previous Ecstasy use (more than 3 times) in a double-blind randomized study, participants were asked to identify 2.0 mg/kg MDMA HCl and serotonergic drug meta-chlorophenylpiperazine (mCPP), which has both serotonin releasing and post-synaptic effects. At 1 to 2.1 mg/kg MDMA HCl, 80% of participants identified MDMA as an empathogen or hallucinogen and only 20% identified MDMA as a stimulant [234]. In contrast, results were mixed with 0.25 to 0.75 mg/kg mCPP, with results varying from hallucinogen to stimulant to sedative depending on the dose. On the "drug liking" visual analog scale (VAS), 1.6 mg/kg ($p < 0.004$) and 2.1 mg/kg MDMA HCl ($p < 0.008$) were significantly higher than placebo, whereas mCPP ratings were not significantly higher than placebo at any dose [234]. In another study in a sample of 74 largely drug-naïve participants receiving MDMA in a controlled laboratory setting, Liechti and colleagues stated that "none of the participants expressed any interest in taking MDMA as a recreational drug" after receiving MDMA [12]. Collectively, these findings support the interpretation that MDMA received in controlled settings is inherently different than MDMA taken in recreational settings, and abuse liability of MDMA-assisted therapy should be evaluated in its intended setting and population for clinical use.

6.8 Impairment

Significant impairment at most of the proposed doses is not anticipated. Nonetheless, participants must not operate a vehicle or any machinery at the end of each study visit and must agree to be driven home following any dosing, as per the clinical trial protocol.

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