Rick Doblin, Ph.D., Testimony to US Sentencing Commission Re: MDMA

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I. Introduction

For the last 35 years, from 1982 when I first learned about MDMA to 1986 when I founded the non-profit research and educational organization, the Multidisciplinary Association for Psychedelic Studies (MAPS), my life has been focused around understanding the therapeutic potential of MDMA and developing MDMA-assisted psychotherapy into an FDA-approved treatment available by prescription. In 2001, I testified before the USSC regarding MDMA, only to see the penalties increased based on risk estimates that seemed excessive at the time; subsequent research ultimately demonstrated a lower risk profile. I'm deeply grateful for this new opportunity sixteen years later to present this written and oral testimony to the USSC to aid in its deliberations reviewing the current sentencing guidelines.

II. The Creation & Criminalization of MDMA

a. Origin of MDMA

MDMA was discovered and patented by the German pharmaceutical company Merck in 1912. MDMA was manufactured as part of a series of chemical intermediates. Merck's goal was to create a new chemical pathway to avoid a competitor's patent in an effort to develop a medicine for uncontrolled bleeding. Merck first tested MDMA in animals in 1927 and found nothing of interest, and never tested MDMA in humans. MDMA is now off-patent.[1]

In 1953-54, MDMA was one of eight compounds studied in animals with funding from the US Army Chemical Center. This research was declassified in 1969 and published in 1972. In 1967, a biochemist formerly employed by Dow Chemical named Alexander Shulgin re-synthesized MDMA after being introduced to the substance at a conference. He provided initial reports of its pharmacology, with 80 mg to 160 mg required to produce desired subjective effects in humans.[2] MDMA was found to robustly influence human emotional status in a unique way without adversely affecting physiological functions or perception, such as visual perception or cognition.[3]

After being rediscovered, MDMA was used as an adjunct to psychotherapy. In 1977, Shulgin introduced a psychologist named Leo Zeff to MDMA. At the time, MDMA was a legal compound only known to a small group of psychopharmacologists. Zeff incorporated MDMA into his psychotherapy practice and ultimately shared MDMA widely with therapists across the country, introducing the substance to hundreds of therapists over the course of years.[4] As reported

[1] Ronald Freudenmann, *et al.*, *The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents*, 101(9) Addiction 1241 (2006).
[2] Shulgin, Alexander & Anne, *Pihkal: A Chemical Love Story*, Transform Press (1991), 69. ISBN: 0-9630096-0-5.
[3] MDMA Investigator's Brochure, 8th Ed. (30 March 2016) ("IB") at 10 (citations removed) [Appendix A].
[4] *Id*.

by the National Institute on Drug Abuse (NIDA) website, some MDMA therapists at the time even called MDMA "penicillin for the soul" because it was perceived to enhance communication in patient sessions and reportedly allowed users to achieve insights about their problems.[5] Chemists and therapists distributing the legal compound hoped to make a meaningful contribution to people's psychological health. Dozens of known therapeutic uses of MDMA are recorded in the public domain so use patents are not available.

Based on my conversations in the early to mid-1980s with MDMA therapists and with chemists producing MDMA for therapists, I estimate about half a million doses of legal MDMA were distributed from the late 1970s to 1984 for use in therapeutic and personal growth settings, without attracting attention of the police. However, in the early 1980s, MDMA began to be marketed outside of therapeutic contexts by entrepreneurs who rebranded MDMA as "Ecstasy" in the club scenes in Dallas, Los Angeles and elsewhere. This campaign initiated recreational use.[6] It was apparent to those using MDMA in therapeutic contexts that the recreational use of MDMA was going to lead to the criminalization of MDMA for all uses, since at the time Nancy Reagan was simultaneously re-escalating the United States' "war on drugs." In 1984, Senator Lloyd Bentsen of Texas requested that the DEA schedule and criminalize MDMA, starting in motion the ending of MDMA's status as a legal substance.

b. History of Criminalization

The DEA first proposed to place MDMA in Schedule I in July of 1984.[7] In response, with the help of pro-bono legal services, I helped organize a group of psychiatrists and psychotherapists to request DEA Administrative Law Judge (ALJ) hearings seeking to maintain MDMA's legal medical use. These hearings were granted and began in early 1985. In the midst of the DEA hearings, which generated media attention that was generally positive about the effects of MDMA, DEA's Acting Administrator John Lawn placed MDMA on Schedule I using emergency scheduling powers, based on a perception of a "continuing and apparently increasing number [of people] being exposed to MDMA, its potential neurotoxicity and the lack of accepted medical use or established safety for use of MDMA."[8]

In 1986, the World Health Organization (WHO) of the United Nations followed the United States' criminalization process, placing MDMA in Schedule I. However, Dr. Paul Grof, the chairman of WHO's Expert Committee on Drug Dependence that reviewed the data on MDMA, voted against the recommendation for criminalization due to concerns that premature scheduling could negatively impact research into MDMA's risks and benefits. The only scientific evidence referenced by the Expert Committee as the basis of the scheduling recommendation was research on a related but different compound, MDA, administered to rats in frequent and high doses. The

[5] A Brief History of MDMA. NIDA. Found at: https://www.drugabuse.gov/publications/research-reports/mdma-ecstasy-abuse/brief-history-mdma.
[6] *Id.*
[7] 49 Fed. Reg. 30210-30212 (July 27, 1984).
[8] DEA Press Release on Emergency Scheduling. May 31, 1985. Found at: http://www.maps.org/research-archive/dea-mdma/pdf/0180.PDF.

World Health Organization (WHO) noted that there was insufficient data to draw strong conclusions: "No data are available concerning [MDMA's] clinical abuse liability, nature and magnitude of associated public health or social problems."[9] The WHO Expert Committee on Drug Dependence, despite its chairman's objections, determined that there was inadequate research supporting MDMA's therapeutic use,[10] though it had been used therapeutically, outside of research, for over a decade. However, the Committee noted in its report that it was impressed by the non-clinical reports of MDMA and urged countries to pursue further research.[11]

In May 1986, after two years of hearings, DEA ALJ Francis Young recommended *against* placing MDMA on Schedule I. He disagreed with the DEA's claim that FDA approval of a drug was "binding on the medical profession which respect to what is, or is not, accepted medical… use."[12] Specifically, he acknowledged that the nonexistence of a New Drug Application (NDA) did not preclude the drug from having medical use.[13] The Opinion also acknowledged MDMA's past use in therapy, and recommended that MDMA be placed in Schedule III.

Despite the weight of the evidence undermining MDMA's placement in Schedule I, and the fact that the DEA had acted outside of its authority when it Emergency Scheduled MDMA, Lawn overruled ALJ Young and classified MDMA as Schedule I in October of 1986.[14]

In 1987, Dr. Lester Grinspoon, a psychiatrist on the faculty of Harvard Medical School, sued the DEA on the grounds that DEA had ignored MDMA's medical use, and the federal court agreed, finding Lawn's ruling "unpersuasive."[15] This decision vacated MDMA's schedule I status. A month later, DEA Administrator Lawn intervened *again* and reverted MDMA to its Schedule I placement, dismissing the expert testimony of psychiatrists discussing over 200 cases of MDMA-assisted psychotherapy because they were not published in medical journals.

It is notable that subsequent to the first emergency placement, the DEA arrested several individuals for MDMA distribution. The DEA claimed that its emergency scheduling authority was derived from the Comprehensive Crime Control Act (CCCA), which Congress passed in 1984. The CCCA granted the Attorney General powers to temporarily schedule drugs without following regular procedures when there was imminent risk to public health. However, the Attorney General

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[9] World Health Organization, *22nd report of the Expert Committee on Drug Dependence*, Technical Report Series (1985) at 25. Found at: http://apps.who.int/iris/bitstream/10665/39635/1/WHO_TRS_729.pdf.
[10] *Id.*
[11] *Id.* at 26 (Despite insufficient methodologically sound data to reliably comment on MDMA's purported therapeutic usefulness, the report stated that "There was...sufficient interest expressed to recommend that investigations be encouraged to follow up these preliminary findings. To that end, the Expert Committee urged countries to use the provisions of article 7 of the Convention on Psychotropic Substances to facilitate research on this interesting substance.")
[12] In the matter of MDMA Scheduling, Docket No. 84-48 (Dec. 2, 2014).
[13] Young stated: "If this is the criterion, 'accepted safety' for use by physicians is reduced to being determined by… a businessman's or corporation's determination of the economic feasibility of mass production. Congress has not given the slightest hint of an intention to rely here on such judgments. That would, however, be the bottom line result of the Agency's position in many cases.... It ignores the reality that commercial pharmaceutical manufacturers base their production decisions on economic considerations. If they are commercially manufacturing a product, they have, no doubt, concluded that the pharmaceutical can be safely used. But the converse is not necessarily true." *Id.*
[14] 51 Fed. Reg. 198, 36552 (October 14, 1986).
[15] *Grinspoon v. DEA*, 828 F.2d 881 (1st Cir., 1987).

had never formally sub-delegated these "emergency scheduling" powers to the DEA. In 1988, three individuals who had pled guilty to distribution of MDMA challenged the emergency scheduling procedure. Based in part on the discrepancies in amount of due process required for the two scheduling procedures, the US Court of Appeals for the Ninth Circuit ruled that DEA's emergency scheduling of MDMA was illegal, freeing the arrested individuals on procedural grounds.[9]

III. The MDMA Sentencing Guideline Lacks An Empirical Basis.

a. Two federal courts have found the 2001 MDMA Sentencing Guidelines to be excessive.

In 2011, at sentencing in two separate federal MDMA trafficking cases, Hon. William Pauley III from the Southern District of New York and Hon. Ricardo S. Martinez from the Western District of Washington, both chose to vary downward from the MDMA Guideline range. In collaboration with MAPS,[16] ACLU attorneys Jay Rorty and Scott Michelman argued that because the MDMA guideline was based on now-discredited science, it lacked an empirical basis and thus need not be adhered to.[17] The courts agreed, acknowledging the 2001 Sentencing Commission's reliance on exaggerated, scientifically unsound perceptions of MDMA's harmfulness.

When sentencing the defendant in *US v. McCarthy*, Judge Pauley adopted an MDMA-to-marijuana ratio of 200:1, higher than the pre-2001 ratio of 35:1 but lower than the present ratio of 500:1.[18] In his Opinion, Judge Pauley concluded that MDMA is not in fact more harmful than cocaine (as concluded by the Sentencing Commission in 2001), but also that it is not as harmful as marijuana.[19] Specifically, he noted that failing to recognize the totality of cocaine's effects, which "render it significantly more harmful than MDMA," led to an imbalanced analysis which did not include multiple factors that could have led to a lighter sentencing determination.[20] In addition, Judge Pauley concluded that the Commission's analysis of MDMA's actual negative impacts - which focused on neurotoxicity alone - was "selective and incomplete."[21]

In *US v. Phan*, the court was not considering imposing a sentence above 36 months, already lower than the 41- to 188-month range which was otherwise possible given the pre-2001 Guideline.[22] However, despite already planning on a downward deviation from the Guideline,

[16] MAPS/ACLU Sentencing Press Release [Appendix D]
[17] *US v. Phan* (W.D. WA 2011), Supplemental Sentencing Memorandum ("*Phan* memo") at 8 [Appendix B].
[18] *US v. McCarthy* (S.D. NY 2011), Memorandum and Order ("*McCarthy* order") at 8 [Appendix C].
[19] *Id*. at 8.
[20] *Id*. at 7.
[21] *Id.* at 5.
[22] *US v. Phan* (W.D. WA 2011), Sentencing Hearing Transcript at 4-5 ("If this court were to treat MDMA as equivalent to marijuana on a ratio of one-to-one, then the resulting level in this case would start at 20. With the appropriate adjustments as set out in the presentence report that's prepared by probation, the end result would be a level 22. This defendant falls in a criminal history category one. His resulting range would then be 41 to 51 months.

Judge Martinez nonetheless acknowledged the need to re-evaluate the guideline ranges in the face of new experience and knowledge.[23] Ultimately, Judge Martinez noted:

> The exact question of whether or not this court believes that there is a problem with the current MDMA guideline I think is before this court, and I believe the answer is, yes, there is. Based on everything that I have seen that was presented here, based on the arguments that were made in the Southern District of New York [*US v. McCarthy*], I think it's imperative that the Sentencing Guideline Commission address this issue, just like they did with disparity between crack and powder cocaine.[24]

b. As successfully argued by the ACLU, the present MDMA Sentencing Guideline is based on inaccurate science.

The sentencing memo submitted to the court in *US v. Phan* provides a thorough overview and rebuttal of the now-discredited science relied on to form the 2001 MDMA Guideline.[25] The memo notes that the Commission's scientific evidence exhibited a number of problems including inadequate controls, inappropriate doses, non-replicable studies, and most notably, research by a researcher who later retracted another study claiming that MDMA caused Parkinson's because the study mistakenly used *d-methamphetamine,* an entirely different compound than the purported MDMA.[26] The *Phan* memo states:

> Specifically, when considering the guidelines for MDMA, the Commission's 'empirical data' included case studies of individuals who were heavy users of other drugs; studies in which animals were administered doses that we now know are exponentially larger relative to their size than doses human beings ingest; a website that the Commission itself noted was not scientific; and the work of a

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If the court were instead to use the ratio of 35-to-one, because that was my understanding of the pre-2001 -- the ratio that was used prior to the 2001 amendments to the current MDMA guidelines, then the resulting guideline range for this defendant, Mr. Phan, would be level 34 and call for a range of 151 to 188 months.").

[23] *Id*. at 6-7. ("I think the fact that the Ninth Circuit has explained that district judges are at liberty to reject any guidelines on policy grounds, and the Ninth Circuit has also held that it would be error to attach a presumption of reasonableness to the guideline range, in view of all that, the court is not required to embrace any particular alternative ratio, and this court will not do so in this situation for a variety of reasons. One, I will not do it because it's not necessary in this case in order for the court to impose a sentence that is sufficient, but not more than necessary to accomplish the reasonable objectives of sentencing. But I do it for another reason that's even more important. The court agrees that there may very well be problems with the MDMA guidelines as currently constructed. As we learn more about the effects of certain drugs on humans, especially after years of experience with those drugs and especially as more designer drugs come into play, it obviously makes logical sense to go back and re-evaluate all the guideline ranges.")

[24] *Phan* memo at 7-8.

[25] *Id.* at 15.

[26] *Id.*

> researcher who subsequently retracted multiple MDMA studies because he was testing the wrong chemical compound.[27]

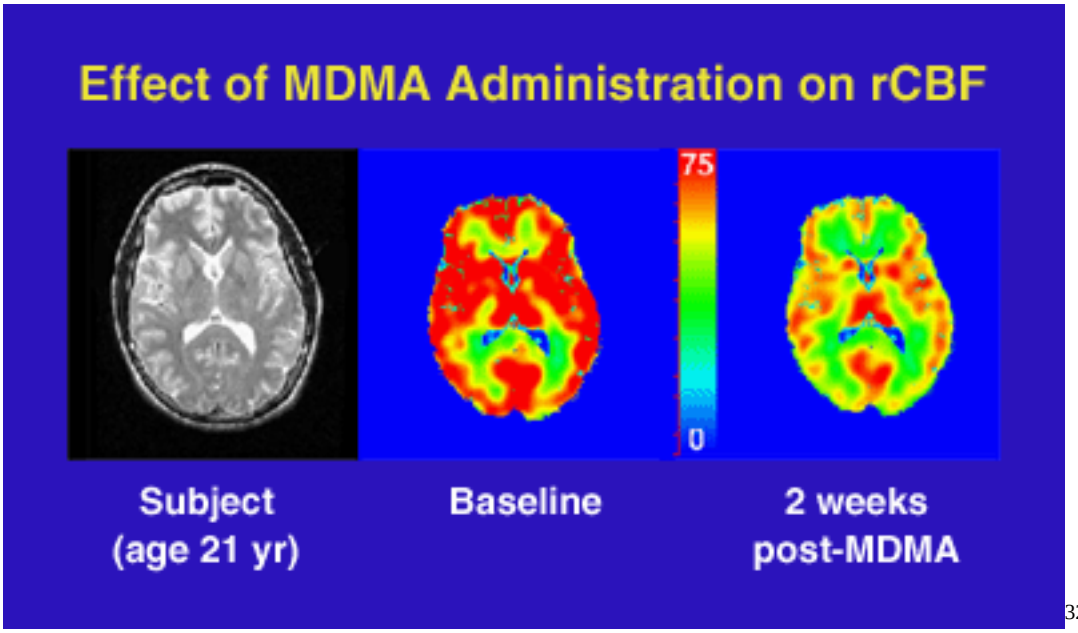
It is also notable that the *Phan* memo compared the discrepancy between fact and reality of MDMA's harmfulness to the discrepancy regarding the crack cocaine guideline at issue in *US v. Kimbrough.*[28] In other words, the Commission's formulation of the Guideline for MDMA sentences, similar to its original formulation for crack cocaine, is based on alarmist and now discredited studies.

In 2004 I published a rebuttal to a number of arguments and studies used to justify MDMA's continued criminalization, including studies used to the 2001 guidelines.[29] For example, then-NIDA Director Alan Leshner's 2001 Senate Subcommittee on Government Affairs testimony was incredibly misleading; Leshner led the Senators to believe that MDMA caused permanent changes in cerebral blood flow, but in fact, the changes were both temporary and of no clinical consequence. As I explain in my 2004 rebuttal in more detail:

> Testimony that then-NIDA Director Alan Leshner gave on July 30, 2001 to the Senate Subcommittee on Government Affairs, illustrated with a large poster purporting to show that MDMA negatively affects (reduces) cerebral blood flow, was clearly misleading. The poster [below, 31] showed a healthy-looking brain with what was represented as normal cerebral blood flow, with this image labeled "Baseline." For comparison purposes, the poster also contained a second brain scan image of the same subject with reduced cerebral blood flow. This image was labeled "Two weeks post-MDMA." What Leshner didn't tell the Senators is that the scans were drawn from a study that showed no difference between Ecstasy users (N=21) and controls (N=21) in cerebral blood flow (Chang et al. 2000).[30]
>
> The images Leshner used in his Senate testimony came from one of the subset (N=10) of the Ecstasy users in the larger study who participated in Dr. Grob's Phase I MDMA safety study. These ten subjects were scanned at baseline, like the other eleven Ecstasy-using subjects in Dr. Chang's research. They were then scanned again after receiving two doses of MDMA administered in the context of Dr. Grob's study, at time points ranging from two weeks to 2-3 months after the last dose of MDMA. Subjects scanned two weeks after MDMA showed a temporary reduction in cerebral blood

[27] *Id.*
[28] *Id.* at 8-10.
[29] Doblin, Rick, *Exaggerating MDMA's risks to justify a prohibitionist policy*, MAPS Research Archive (January 16, 2004) ("Doblin 2004"). Found at: http://www.maps.org/research-archive/mdma/rd011604.html.
[30] Chang, et. al., *Effect of ecstasy 3,4-methylenedioxymethamphetamine / MDMA on cerebral blood flow: a co-registered x SPECT and MRI study*, Psychiatry Research: Neuroimaging Section 98 (2000), 15-28.

flow while subjects scanned from 2-3 months after MDMA showed a return to baseline. The impression Leshner left the Senators was that MDMA caused permanent changes in cerebral blood flow when the changes were both temporary and of no clinical consequence.[31]

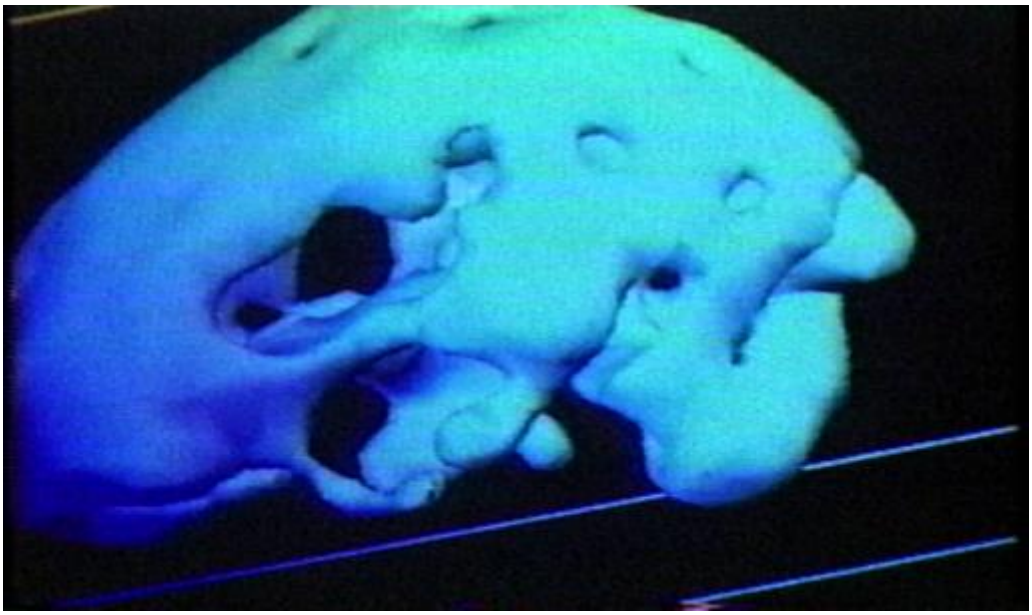


[32]

Ironically, Leshner didn't realize that in order to participate in the Phase 1 study and receive MDMA, FDA required subjects to have already had substantial exposure to MDMA. On average, the subjects in Dr. Chang's study had an exposure to MDMA of 211 times. Thus, the healthy-looking brain that Leshner showed to the Senators to contrast with the image of the same brain two weeks post-MDMA was actually the brain of a heavy MDMA user at baseline! If he had fully understood the science underlying the images he showed to the Senator, Leshner should have reported that the baseline image dramatically illustrated that MDMA caused no persisting long-term differences in cerebral blood flow as compared to the non-MDMA using controls. Instead, he used the image to convey an impression of the dangers of MDMA at odds with what the study actually demonstrated.

[31] Leshner, Alan, Hearing Before the Senate Subcommittee on Governmental Affairs - "Ecstasy Abuse and Control" Statement for the Record (July 30, 2001). Found at: http://www.drugabuse.gov/Testimony/7-30-01Testimony.html.

[32] Image originally found at: https://archives.drugabuse.gov/Testimony/7-30-01Testimony.html.



My rebuttal also addressed the misleading and alarmist myth that MDMA causes "holes" in user's brains. I wrote:

> Frightening and disturbing images of the brain of an MDMA user that showed explicit holes in the brain [above] that were claimed to have been caused by MDMA have been shown on an MTV special documentary about Ecstasy, as well as on an Oprah Winfrey show. These images were graphically manipulated to represent areas of lower cerebral blood flow as holes and are completely fraudulent. According to a March 2001 educational program about drugs aimed at young people that NIDA helped create, Alan Leshner stated, "We've heard people talk about Ecstasy causing holes in the brain and of course that's a bit of an exaggeration, but there is a core truth to it."[33]

The *Phan* memo provides another example of similarly problematic science: a leading MDMA neurotoxicity researcher, with federal funding from NIDA, published numerous retractions after admitting to mistakenly researching methamphetamine, not MDMA. The *Phan* memo explains:

> The Commission also relied on several studies that were not able to be replicated, or scientists whose work was fraught with methodological problems. For instance, Dr. George Ricaurte, cited and relied upon as '[a] leading researcher in MDMA toxicity studies' in the Commission's 2001 report to Congress, had to

[33] Doblin 2004.

> retract multiple studies after it was discovered that they had not been done with MDMA, but with mislabeled vials of methamphetamine. After this error came to light, in 2003 the journal Science retracted a Ricaurte study purporting to show that a single dose of MDMA could cause brain injury. The mislabeled vials corrupted several of Ricaurte's other studies, as well, and he was forced to withdraw four other papers. Even scientists Ricaurte named in defense of his work were quoted in the New York Times as saying that "some of his best-known work has nonetheless been 'sloppy' or 'not as methodologically rigorous as you might want."[34]

From 1989-2002, Drs. Ricaurte and McCann received federal grants totaling over $14.6 million dollars for MDMA and MDMA-related research.[35]

At my USSC testimony in March 2001, I opposed increasing penalties for MDMA for two primary reasons. The first was that enhanced penalties would increase difficulties in obtaining FDA and DEA permissions to conduct legitimate scientific research into the risks and benefits of the therapeutic use of MDMA as an adjunct to psychotherapy. The second, which is particularly relevant to this testimony, is that MDMA's risks have been greatly exaggerated, particularly the risk of serious functional or behavioral consequences from MDMA neurotoxicity.

USSC's sharp increase in mandatory minimum sentences for MDMA crimes in 2001, from a 35:1 to a 500:1 marijuana-to-MDMA ratio, reflects the hysteria, not the science, much like the circumstances responsible for MDMA's criminalization in the first place. Today, even more data is available to rebut the exaggerated claims of the past.

c. Most commonly cited MDMA neurotoxicity studies are misleading.

Animal studies that demonstrated MDMA to be neurotoxic were using extremely high doses of MDMA, not at all comparable to doses commonly used in humans. These studies administered multiple doses 50 to 100 times higher than doses used in human clinical trials, if appropriate allometric scaling is used between species. Serotonergic toxicity has not been found with doses close to the range used in clinical and recreational use.[35] However, as the MAPS Investigator's Brochure, a literature review of over 600 relevant MDMA studies, writes:

> Repeated very high doses of MDMA in animals reduce total serotonin levels in the brain, impair transport of serotonin, and cause psychobehavioral changes such as increased anxiety...However, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses, with findings now clearly indicating that doses used in nearly all rat and most primate studies

[34] *Phan* memo at 18 (citations omitted).
[35] Jerome, Ilsa, Ph.D., *NIDA and NCRR Funding for Ricaurte and McCann 1989-2003*, MAPS (2004). Found at: http://www.maps.org/research-archive/mdma/ricaurtefunding.pdf.

> are inappropriately high for comparison to use in clinical settings and are more pertinent toxicological effects of MDMA.[36]

In addition, the "timebomb" theory of MDMA neurotoxicity was premised on the belief that MDMA neurotoxicity was indeed harmful; but not because of MDMA's acute or short-term effects, but rather for effects that some predicted would only show up later in life, perhaps 25 years from when the MDMA was actually being used. However, more than 25 years have passed since those claims were made and we can see now that those fears have not been actualized.

III. MDMA's Robust Prosocial Capacity and Low Risk Profile

a. MDMA's Risk Profile

Analysis and research compiled in MAPS Investigator's Brochure suggests that MDMA's physiological effects are mild when consumed at common recreational and therapeutic doses, and "likely to be well tolerated by healthy individuals."[36] These physiological impacts rarely reach "elevations that exceed those seen after moderate exercise."[37] Negative effects include "lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, headache, impaired gait or balance, muscle tension, ruminations, feeling cold, and thirst," as well as a mild immunosuppressant effect.[38]

However, MDMA combined with aerobic dancing, a hot crowded environment and not drinking enough water, can become a lethal mix, sometimes resulting in heatstroke. A standard dose of MDMA raises body temperature about one degree, and also inhibits the body's natural thermoregulation, increasing likelihood of heatstroke. Heatstrokes can be easily avoided with the implementation of basic harm reduction measures like access to free water or "cool down rooms." Very rarely, Ecstasy users drink too much water and die from hyponatremia, preventable by substituting drinks with electrolites like Gatorade or fruit juices instead of water.

Black-market MDMA possesses a higher risk profile than responsibly-dosed, pure MDMA. The risks of consuming illicit MDMA include: taking MDMA in an unsafe physical or psychological setting, insufficient knowledge about MDMA, insufficient access to basic harm reduction measures, ingesting a more dangerous substance that is sold as (but is not actually) MDMA, and risks associated with contact with law enforcement. *These risks, however, are all the result of MDMA's criminalization, not MDMA itself.*

MAPS has developed an expertize in minimizing the harms of problematic use of psychedelic substances. MAPS sponsors a program called the Zendo Project, which supports

[36] IB (*supra* note 3) at 9.
[37] *Id.*
[38] *Id.*

medical and emergency teams at large festivals and events across the United States and the world by working with people having difficult psychedelic experiences, commonly known as "bad trips." Instead of being arrested by police or tranquilized by medical staff unfamiliar with psychedelic experiences, the Zendo Project provides a supportive space and peer-counselors specially trained to de-escalate challenging psychedelic experiences, and ultimately transform them into valuable healing and growing opportunities. The Zendo Project has supported almost 2,000 people[39] through difficult psychedelic experiences. Notably, MDMA produces far fewer difficult psychological experiences than substances such as LSD, despite MDMA being more popular. At Burning Man, a festival that hosts 70,000 attendees for a week in the Nevada desert, approximately 6% of Zendo's drug-related intakes in 2016 were related to MDMA.

MDMA is not and has never been the dangerous drug it was once made out to be. Emergency room statistics from 2011 - the most recent publicly available data - show that MDMA-related emergency department visits only amounted to only 1.8% of drug or alcohol-related visits that year.[40] A majority of these visits were inspired by acute psychological distress, and most cases were resolved after supportive care.[41] Further, between 2013 and 2016, the rate of MDMA use in young people has decreased.[42] The social harm from MDMA use is small, and although its use does come with certain risks, they can be significantly mitigated or eliminated with education, harm reduction, and decriminalization.

b. MDMA literature reviews highlight MDMA's prosocial capacities.

In July 2016, the peer-reviewed scientific journal Cell published a commentary about current research into the use of MDMA as a probe for social behaviors and as an adjunct to psychotherapy. The article, authored by neuroscientists Boris Heifets, M.D., Ph.D., and Robert Malenka, M.D., Ph.D., of Stanford University, summarizes current knowledge about MDMA's mechanism of action, highlighting its ability to catalyze prosocial, empathogenic effects. The authors of the Cell article write:

> Here, we argue for the importance of using all the available tools of modern basic and clinical neuroscience research to maps MDMA's mechanism of action in the brain.
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> [...]
>
> While such pragmatic clinical studies will certainly be important, we are equally excited about the utility of MDMA as a unique and relatively simple manipulation that can be used to probe the neural

[39] Since 2012, the Zendo Project has assisted 1,986 guests and trained approximately 1,166 volunteers, and trained hundreds more in the principles of psychedelic peer counseling.
[40] Drug Abuse Warning Network, *2011: National Estimates of Drug-Related Emergency Department Visits*. HHS (2011). Found at: http://archive.samhsa.gov/data/2k13/DAWN2k11ED/DAWN2k11ED.htm.
[41] IB (*supra* note 3) at 32.
[42] *Monitoring the Future Study: Trends in Prevalence of Various Drugs*. NIDA (2013-2016). Found at: https://www.drugabuse.gov/trends-statistics/monitoring-future/monitoring-future-study-trends-in-prevalence-various-drugs

> basis of prosocial behaviors in a wide range of species.
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> [...]
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> As a probe of brain function, [MDMA] is a remarkably simple but powerful tool that can be used to advance our understanding of the neural basis of empathy, social reward, and related prosocial behaviors. Such understanding can only benefit individuals and the human interactions in which they engage. The world's populations need more compassion and empathy for one another. The study of MDMA provides one small but potentially important step toward reaching that goal.[43]

MAPS has also compiled and published a comprehensive Investigator's Brochure, which is a summary and analysis of the world's relevant, peer-reviewed literature about MDMA. MAPS published the Eighth Edition of the IB in March 2016.[44] The Investigator's Brochure includes a number of notable findings, a short excerpt of which is quoted below:

> The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, and make unpleasant memories less disturbing while enhancing communication and capacity for introspection. These factors taken together can provide the opportunity for a corrective emotional experience in the context of psychotherapy. Many of the therapeutic effects of MDMA-assisted psychotherapy are evident within a short period of treatment, often after the initial session.
>
> Increased feelings of interpersonal closeness, changes in social perception and reduced anxiety may make MDMA a suitable pharmacological adjunct to enhance psychotherapy for anxiety disorders, such as PTSD and social anxiety in autistic adults. MDMA may provide a much needed option in the treatment of PTSD and anxiety associated with other conditions. Published results from MAPS study (MP-1) showed clinically and statistically significant improvements in PTSD severity in 20 per protocol subjects. Findings from the long-term follow-up of MP-1 suggest that therapeutic benefits were sustained for an average of 41 months post-treatment. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) demonstrated clinically significant improvements in PTSD symptoms, with results in the 125 mg MDMA dose group numerically but not statistically superior to the

[43] Heifets, Boris, M.D., Ph.D., and Malenka, Robert, M.D., Ph.D., *MDMA as a Probe and Treatment for Social Behaviors*, Cell (July 14, 2016) ("Heifets"). Found at: http://www.cell.com/cell/fulltext/S0092-8674(16)30853-4.
[44] IB (*supra* note 3).

> 25 mg MDMA dose group. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. There were no drug-related Serious Adverse Events (SAEs) or safety concerns in either study.
>
> Data from MAPS studies and published literature show that MDMA produces sympathomimetic effects that...are likely to be well tolerated by healthy individuals. Most people do not experience elevations that exceed those seen after moderate exercise….Common reactions reported in the literature and clinical trials from MDMA are transient and diminish as drug effects wane during the session and over the next one to 7 days…. Due to [the limited duration of listed effects,] these sub-acute reactions are not likely to have clinical significance.
>
> As of 01 October 2015, with 1180 individuals exposed to MDMA in controlled research settings (which includes 122 in MAPS-sponsored studies), there have been no unexpected drug-related SAEs to date, and expected SAEs have been rare and non-life threatening.[45]

In sum, there is evidence that MDMA can result in increased compassion, decreased anxiety, and a change in perception that combines effectively with psychotherapy to produce fertile grounds for personal healing and development. Results from MAPS-sponsored research with MDMA-assisted psychotherapy for PTSD is particularly encouraging. At this time, MAPS has completed Phase 2 investigations of MDMA-assisted psychotherapy for PTSD, we are now preparing to begin Phase 3.

c. MAPS has sponsored and published FDA-approved studies demonstrating the healing capacity of MDMA-assisted psychotherapy in clinical settings.

Since 2001, MAPS has sponsored nine FDA-approved drug development studies evaluating the efficacy of MDMA-assisted psychotherapy for psychiatric disorders including PTSD, anxiety associated with a life threatening illness, and social anxiety in autistic adults, at research sites across the United States and around the world. MAPS' FDA-approved clinical trials have demonstrated that MDMA, in conjunction with psychotherapy, has promising therapeutic capabilities. In November 2016, the Food and Drug Administration approved a large-scale, Phase 3 trial of MDMA-assisted psychotherapy for chronic PTSD, the final phase of research required for full FDA-approval for MDMA-assisted psychotherapy. If Phase 3 follows Phase 2's success, the trial would trigger MDMA's rescheduling, as MDMA would no longer qualify for Schedule I with "no accepted medical use."

[45] IB (*supra* note 3) at 9.

FDA's green light for Phase 3 MDMA/PTSD studies was based on the results of a meta-analysis from Phase 2 MDMA/PTSD pilot studies in 107 subjects: in all participants' evaluated so far for the 12-month follow up after experiencing MDMA-assisted psychotherapy for PTSD (N=86), 67% of participants no longer met PTSD diagnostic criteria. For comparison: the only medications currently FDA-approved to treat PTSD, Zoloft and Paxil, are approximately 50% effective at reducing symptoms of PTSD, but not eliminating them. In one small MDMA-assisted psychotherapy pilot study in Charleston, South Carolina, 83% of participants no longer qualified for PTSD,[45] and three-quarters of participants sustained their PTSD-free results three and a half years later.[46]

A MAPS pilot study evaluating MDMA-assisted psychotherapy for the treatment of social anxiety in autistic adults has produced promising results that support a large effect size in treating social anxiety symptoms, with data being prepared for a scientific paper to be submitted for publication. Results are not available for our study of MDMA-assisted psychotherapy for anxiety associated with life-threatening diagnoses, but the study is ongoing and a review of the safety data has revealed that MDMA is well-tolerated in this population.

MDMA-assisted psychotherapy works by allowing the participant to address the root cause of his or her trauma in a safe and supportive environment, and re-process that trauma without the debilitating associations of fear and anxiety. MDMA reduces fear activation in the amygdala, which allows participants to revisit past trauma, and develop compassion for themselves.

One study participant, a military veteran named CJ Hardin, explained to the New York Times in November 2016: "[MDMA] changed my life...It allowed me to see my trauma without fear or hesitation and finally process things and move forward…[Before] I just felt hopeless and in the dark...But the MDMA sessions showed me a light I could move toward. Now I'm out of the darkness and the world is all around me."[46]

Another study participant named Julie Nelson, who survived sexual assault, recounts to Elle magazine in March 2017: "[MDMA] was like stepping off a burning tightrope...I always felt shredded internally, and this was the first time I felt whole and soft, and that the world wasn't trying to eat me."[47]

d. Highlights of Non-MAPS MDMA Research

As more MDMA research is published, more institutions continue to show interest in pursuing this promising line of research. MAPS is collaborating with a number of VA therapists across the country and is funding several research pilot projects combining MDMA with existing psychotherapeutic approaches to PTSD including Cognitive Behavioral Conjoint Therapy and Prolonged Exposure. In the U.K. a MAPS-trained psychiatrist is starting a study evaluating MDMA-assisted psychotherapy in the treatment of alcohol use disorder. Yale University's Department of Psychiatry will be starting a study increasing exploration of MDMA's mechanism

[46] Philipps, David. *F.D.A. Agrees to New Trials for Ecstasy as Relief for PTSD Patients*, New York Times (November 29th, 2016). Found at: https://www.nytimes.com/2016/11/29/us/ptsd-mdma-ecstasy.html?_r=0.
[47] Kamp, Louisa, *Could a Club Drug Be The Secret to Curing PTSD?* Elle Magazine (March 1, 2017). Found at: http://www.elle.com/culture/a43266/mdma-ecstasy-molly-ptsd-treatment/.

of action, with a focus on fMRI neuroimaging research in people with PTSD after they have taken MDMA. NIDA has provided grants to the University of Chicago Psychiatry and Behavioral Neurosciences Department to conduct studies of MDMA and emotional processing. Two such studies, which draw conclusions about MDMA's prosocial capacities, are summarized here:

One study, entitled "MDMA decreases the effects of simulated social rejection," concluded:

> Our finding that MDMA decreases perceptions of rejection in simulated social situations extends previous results indicating that MDMA reduces perception of social threat in faces. Together these findings suggest a cognitive mechanism by which MDMA might produce pro-social behavior and feelings and how the drug might function as an adjunct to psychotherapy. These phenomena merit further study in non-simulated social environments.[48]

A second study entitled "MDMA alters emotional processing and facilitates social interaction" concluded:

> MDMA alters basic emotional processes by slowing identification of negative emotions and increasing responses to positive emotions in others. Further, it positively affects behavior and perceptions during actual social interaction. These effects may contribute to the efficacy of MDMA in psychotherapy, but appear less closely related to its abuse potential.[49]

e. Non-clinical MDMA use can produce self-healing.

While non-clinical use of Ecstasy can be problematic for some people, and in rare instances even fatal when consumed in certain temperature-elevated settings without harm reduction services , there are also thousands of people who have experienced healing benefits from MDMA even when taken outside of clinical settings. There are numerous anecdotal accounts of self-medication and self-healing posted on the internet. Multiple short documentaries have been produced detailing the experiences of veterans who cured their own PTSD with MDMA.[50] MAPS has heard hundreds of anecdotes of personal accounts from people who have used MDMA to heal from a number of other mental and physical health disorders, ranging from eating disorders to alcoholism; dozens of these accounts have been published on the MAPS website.[51] One such anecdote, written by a woman who used MDMA with her husband to heal from her sexual trauma,

[48] Frye, C.G., M.C. Wardle, G.J. Norman, H. de Wit (2014) MDMA decreases the effects of simulated social rejection. *Pharmacology, Biochemistry and Behavior*, 117, 1-6. PMC3910346
[49] Wardle, M.C., H. de Wit (2014) MDMA alters emotional processing and facilitates social interaction. *Psychopharmacology*. PMC4194242
[50] *See* Ecstatic States, found at: https://vimeo.com/94074343. *See also* Psychedelic Soldiers, found at: https://www.youtube.com/watch?v=hGVaiC0SwsQ.
[51] *Accounts of MDMA's Healing Effects,* MAPS. Found at: http://www.maps.org/research/mdma/104-research/mdma/other-mdma-resources/5401-accounts-of-mdma%E2%80%99s-healing-effects.

is excerpted here:

> My first experience [with MDMA] was marriage-saving and life-changing, allowing me to acquire an emotional bond with my husband through empathy, compassion, and understanding that I had never before experienced, and a "discovery of body", which (after years of sexual dysfunction in our marriage, i.e. painful intercourse only endured with tears streaming out of my eyes and following through out of duty alone, never knowing if I had ever experienced an orgasm,) was beyond words as I experienced sex "how it was meant to be" for the first time ever. I achieved a different perspective on life and a sense of harmony with the universe and that I was wanted and somehow needed on the planet, just enough to give me back the will to live. Little did I know that this was the first step that had to take place in the uncovering of the layers that were built up around at least one sexual trauma in my past; walls so thick that I convinced even myself that the trauma never existed.
>
> […]
>
> This MDMA substance was able to provide the necessary detachment from the physical pain that I needed in order to get in touch with what physically happened, it opened me up to the compassion that I needed to feel towards myself and gave me the courage to accept my own responsibility and why it happened, it provided the confidence I needed to be able to have faith in my own ability to honestly communicate this event to my husband after having lied to him about it for all those years, it gave me faith in his ability to understand and have compassion towards me while at the same time it gave me compassion and understanding towards him for the hurt that he felt from the lies and misrepresentation, and it drove me with a resolve I needed to pursue getting better and to seek out the proper help that I needed to deal more effectively with these issues. This MDMA substance gave me a passion for and a drive toward seeking out the truth about myself and about this event, whereas other prescription anti-depressant and anti-anxiety type drugs that I had taken in the past had killed the memories and "made me happy" in a denial-type, temporary fashion.[52]

[52] Anonymous. *MDMA for PTSD for Violent Sexual Abuse*. Found at: http://www.maps.org/research-archive/mdma/june022704.html. (Note that this was anonymously reported for fear of incrimination).

IV. Conclusion

In sum, the totality of evidence we have available, which is significantly more than there was when the USSC came to its first conclusion - that one gram of MDMA should carry with it the same penalties as 500 grams of cannabis – strongly indicates that the sentencing guidelines are extremely disproportionate and in fact unrelated to MDMA's actual risks. The MDMA Sentencing Guideline should reflect MDMA's actual risk profile, rather than the exaggerated and inaccurate risk profile that it has been presented with in the past.

V. Appendices

APPENDIX A: MDMA Investigator's Brochure, 8th Ed. (30 March 2016) ("IB")

APPENDIX B: *US v. Phan* (W.D. WA 2011), Supplemental Sentencing Memorandum ("*Phan* memo")

APPENDIX C: *US v. McCarthy* (S.D. NY 2011), Memorandum and Order ("*McCarthy* order")

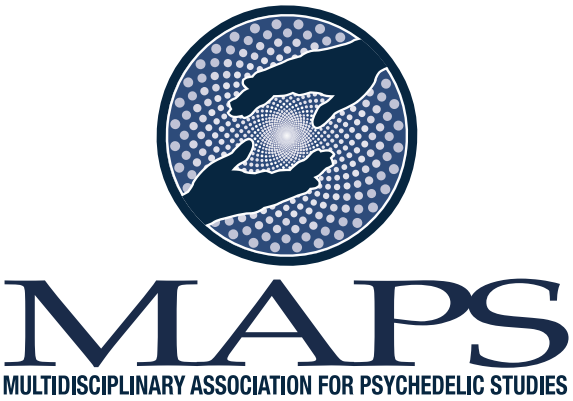
APPENDIX D: MAPS/ACLU Sentencing Press Release

APPENDIX E: Media Highlights

APPENDICES:

APPENDIX A

MDMA Investigator's Brochure, 8th Ed. (30 March 2016) ("IB")



Investigator's Brochure

SPONSOR	Multidisciplinary Association for Psychedelic Studies (MAPS)
PRODUCT	3,4-methylenedioxymethamphetamine (MDMA)
IND #	063384
DATA CUT-OFF DATE	01 October 2015
EFFECTIVE DATE	30 March 2016
EDITION	8th Edition
REPLACES	7th Edition (dated 01 August 2013)

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List of Figures and Tables

List of Abbreviations

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

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

1.0 Summary

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a U.S.-based non-profit research and educational organization supporting research of the therapeutic potential of 3,4-methylenedioxymethamphetamine (MDMA). MAPS is sponsoring clinical trials of MDMA-assisted psychotherapy for patients with chronic disorders such as Posttraumatic Stress Disorder (PTSD), social anxiety associated with autism, and anxiety related to terminal illnesses. MDMA-assisted psychotherapy is an experimental treatment that combines psychotherapeutic techniques with administration of MDMA, a pharmacological adjunct that enhances aspects of psychotherapy. Prior to placement on the Drug Enforcement Administration's (DEA) list of Schedule I substances, MDMA was administered to thousands of people in psychotherapeutic practice outside of clinical trials. According to the 2011 United Nations World Drug Report, 11 to 28 million people aged 15 to 64 used Ecstasy, material represented as containing MDMA, around the world in various non-medical settings [1-5, 631]. The information presented in this Investigator's Brochure (IB) is summarized from published research studies of MDMA conducted by groups outside of the sponsor, sponsor collected data and published studies of Ecstasy use. For the purposes of this document MDMA will be used to refer to drug of known purity used in a controlled setting and Ecstasy will be used to describe drug-related information gathered from epidemiological settings.

MDMA is a ring-substituted phenethylamine also known as methylenedioxymethamphetamine. MDMA is structurally similar, but functionally distinct, from amphetamines. MDMA is a chiral molecule, the sponsor uses racemic MDMA in the form of white crystalline powder compounded with inert material into capsules. The hydrochloride salt of MDMA is readily water soluble and once ionized is lipophilic. A substantial amount of data, both clinical and nonclinical, has been collected for over half a century of research on the physiological and psychological effects of MDMA in humans and animals. Estimates from animal data suggest a median lethal dose (LD50) in humans between 10 to 20 mg/kg [632]. Due to a wide range of responses to identical milligram per kilogram (mg/kg) dosing [7], the sponsor's human trials use fixed doses equivalent to between 1 and 4 mg/kg (active doses in studies range from 75 mg to 225 mg). Onset of MDMA effects occurs 30 to 60 minutes after oral administration [7, 8, 9], peak effects appear 75 to 120 minutes post-drug [10, 11, 12], and duration of effects lasts from 3 to 6 hours [10, 12, 13], with most effects returning to baseline or near-baseline levels 6 hours after drug administration. The elimination half-life of active doses is 8 to 9 hours [14].

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

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

and prosocial effects through release of the monoaminergic neurotransmitters, with the greatest effect on serotonin, followed by norepinephrine and dopamine [21-25]. MDMA has been shown to acutely decrease activity in the left amygdala and increase blood flow to the prefrontal cortex (PFC) in the brain [26-28]. MDMA has also been found to increase serum levels of the neurohormones oxytocin and arginine vasopressin (AVP) in humans [19, 29-33]. Some studies in healthy volunteers suggest that MDMA increases trust and attenuates reactivity to threatening cues, which are at least partially associated with oxytocin release [29, 34, 35]. The combined neurobiological effects of MDMA can increase compassion for self and others, reduce defenses and fear of emotional injury, and make unpleasant memories less disturbing while enhancing communication and capacity for introspection [36-39]. These factors taken together can provide the opportunity for a corrective emotional experience in the context of psychotherapy. Many of the therapeutic effects of MDMA-assisted psychotherapy are evident within a short period of treatment, often after the initial session.

Increased feelings of interpersonal closeness, changes in social perception and reduced anxiety may make MDMA a suitable pharmacological adjunct to enhance psychotherapy for anxiety disorders, such as PTSD and social anxiety in autistic adults [40]. MDMA may provide a much-needed option in the treatment of PTSD and anxiety associated with other conditions. Published results from MAPS study (MP-1) showed clinically and statistically significant improvements in PTSD severity in 20 per protocol subjects [41]. Findings from the long-term follow-up of MP-1 suggest that therapeutic benefits were sustained for an average of 41 months post-treatment [42]. The sponsor's second Phase 2 pilot study conducted in Switzerland (MP-2) demonstrated clinically significant improvements in PTSD symptoms, with results in the 125 mg MDMA dose group numerically but not statistically superior to the 25 mg MDMA dose group [43]. Long-term follow-up data 12 months later suggest that therapeutic benefits continued to increase in this subject population. There were no drug-related Serious Adverse Events (SAEs) or safety concerns in either study.

Data from MAPS studies and published literature show that MDMA produces sympathomimetic effects that include significant transient, self-limiting increases in heart rate (HR) and blood pressure that are likely to be well tolerated by healthy individuals [7, 9, 10, 12, 26, 44-46]. Most people do not experience elevations that exceed those seen after moderate exercise. These results were reproduced in MAPS Phase 1 safety study [47]. Risks posed by elevated blood pressure are addressed by excluding candidates with a history of cardiovascular, cerebrovascular disease, or with pre-existing uncontrolled hypertension and by regularly monitoring blood pressure and pulse throughout experimental sessions. Common reactions reported in the literature and clinical trials from MDMA are transient and diminish as drug effects wane during the session and over the next one to 7 days. The effects include lack of appetite, insomnia, dizziness, tight jaw or bruxism, difficulty concentrating, headache, impaired gait or balance, muscle tension, ruminations, feeling cold, and thirst (see Section 5.3.9 Adverse Events). MDMA is also a mild immunosuppressant [48]. Due to their limited duration, these sub-acute reactions are not likely to have clinical significance.

As of 01 October 2015, with 1180 individuals exposed to MDMA in controlled research settings (which includes 122 in MAPS-sponsored studies), there have been no unexpected drug-related SAEs to date, and expected SAEs have been rare and non-life threatening. As of the data cut-off, a single expected related SAE (increased ventricular extrasystoles), and 10 unrelated SAEs after drug administration have been reported in MAPS-sponsored clinical trials.

There have been a number of SAEs reported in individuals who use Ecstasy (material represented as containing MDMA, as defined above) around the world in various non-medical settings [1-5]. These include fatalities reported after Ecstasy and poly-drug use in unsupervised and uncontrolled

settings. These events are relatively rare given the prevalence of Ecstasy use, estimated to be in the millions worldwide [49, 50]. The most common adverse effects in Ecstasy and poly-drug use include hyperthermia, psychiatric problems, hepatotoxicity, and hyponatremia [51-55] (see Section 4.4 Toxicology in Animals and Epidemiological Settings and 4.5 Serious Reports, Mortality, and Morbidity in Animals and Epidemiological Settings).

2.0 Introduction

MDMA is not a novel compound. The history of its use in humans predates controlled studies in healthy volunteers and clinical trials. MDMA was first synthesized and patented by Merck in 1912 [56] and is currently not covered by a patent. MAPS holds the Drug Master File (DMF) and an Investigational New Drug (IND) for MDMA with the U.S. Food and Drug Administration (FDA). After MDMA was rediscovered by the chemist Alexander Shulgin in 1976 [57], he and his colleagues provided initial reports of its pharmacology, with 80 mg to 160 mg MDMA required to produce desired subjective effects in humans [58, 59]. MDMA was found to robustly influence human emotional status in a unique way [59] without adversely effecting physiological functions or perception, such as visual perception or cognition [8, 11, 13].

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor, with additional effects on limiting neurotransmitter production and degradation. Its prominent effects on serotonin differentiate it from amphetamine and methamphetamine, which primarily act to increase catecholamines such as norepinephrine and dopamine [21, 60]. In the Merck Index, MDMA resides in the Entactogen class [61]. Entactogens contain a ring-substituted amphetamine core, belong to the phenethylamine class of psychoactive drugs, and are described as promoting acceptance and compassion for self and others, changing recognition and response to emotions, and increased interpersonal closeness [19, 37, 62, 63]. In comparison to anxiolytics, antidepressants and atypical antipsychotics, MDMA does not require steady state levels in the blood to function as a catalyst to psychotherapy. Two to six administrations of MDMA, spaced approximately 1 month apart at active doses of 75 mg to 125 mg, may be an alternative to other medications that require daily dosing. This infrequent dosing regimen mitigates adverse event (AE) frequency and improves the risk/benefit ratio of MDMA, which may provide a significant advantage over daily dose medications.

Shulgin and Nichols were the first to report the effects of MDMA in humans [59]. MDMA-assisted psychotherapy first occurred during the mid-to-late 1970s after Shulgin introduced MDMA to a psychotherapist, Leo Zeff. Reported effects of MDMA include enhanced feelings of closeness to others, wellbeing, and insightfulness [64-66]. Prior to placement in Schedule I, MDMA was used in psychotherapy for individuals, couples, and groups to treat diverse psychological disorders, including moderate depression and anxiety [65, 67-69]. It was also found to be useful in reducing physical pain secondary to certain kinds of cancer [68]. No formal controlled clinical trials of safety and efficacy were conducted at the time [65, 70].

During the early 1980s, increasing numbers of people began using MDMA, sold as "Ecstasy" outside of therapeutic contexts [1]. The first wave of non-medical use occurred not only in dance clubs, but also in groups of people who used the drug in a self-exploratory or spiritual context. Non-medical use continues today in the same contexts [4, 71]. In the U.S., an estimated 800,000 people reported initiating Ecstasy use in the past year [72], and approximately 2.1 million Europeans between the ages of 15 and 64, or approximately 0.6% of the population, reported using Ecstasy in 2013 [73].

MDMA was added to the list of Schedule I controlled substances in the U.S. in 1985, defining it as a drug with a high potential for abuse and no accepted medical use [74, 75]. Classification as a Schedule I controlled substance, combined with the early research in animals and recreational users, hampered clinical research into the medical uses of MDMA until the 1990s. Shortly after it was scheduled, animal studies described long-term decreases in markers of serotonergic functioning after high or repeated doses of MDMA administration [76], however these were not relevant to doses in clinical trials [77, 78]. A recently published meta-analysis took careful steps to overcome methodological limitations in previous work, and found only modest indicators of long-term impairment in cognitive function in humans [53]. A systematic review of brain imaging studies in moderate ecstasy users found no convincing evidence for structural or functional changes [79]. Reports of AEs, such as hyperthermia, following Ecstasy use [80-82] and studies in Ecstasy users reporting changes in serotonin transporter (SERT) density, impaired memory and executive function raised concerns regarding the safety of MDMA administration [83-87]. However uncontrolled studies of Ecstasy use and preclinical animal studies that use inappropriately high doses of MDMA produce findings that are open to several interpretations [78, 88]. The vast majority of publications of Ecstasy users are retrospective reports in polydrug-users [53, 89].

While the initial studies in the 1990s conducted in humans examined the physiological effects of MDMA strictly from a safety perspective, current investigations have examined the effects on attention, prosocial effects, memory and brain activity, and human drug discrimination. Findings from an initial sponsor-funded study indicated that MDMA-assisted psychotherapy could be conducted safely in people with chronic PTSD who had failed first line treatments [90, 527]. This was repeated in a chronic, treatment-resistant PTSD sample in a sponsor-supported study (MP-1) [42] which demonstrated durable improvement in PTSD severity, with no difference in cognitive function between placebo and MDMA groups after an active dose of MDMA was given on two occasions, 1 month apart. In addition, placebo-controlled Phase 1 clinical trials confirmed that MDMA produces an easily controlled intoxication characterized by euphoria, increased well-being, sociability, self-confidence, extroversion, transient increases in anxiety, and minor alterations in perception [8, 10-12, 29, 30, 35, 91, 92].

MAPS is completing Phase 2 investigations of MDMA-assisted psychotherapy. Significant durable improvement in PTSD symptoms lasted for at least 12 months after MDMA-assisted psychotherapy in two completed studies (MP-1, MP-2) [42, 43]. There are four Phase 2 studies for treatment of PTSD that have completed treatments and are in follow-up: two studies in the U.S. (MP-8, MP-12), one in Canada (MP-4), and one in Israel (MP-9). Data from Phase 2 studies will be submitted to FDA for an End-of-Phase 2 meeting to support an application for Phase 3 multi-site MDMA/PTSD research studies. Based on the current state of scientific knowledge and the risk/benefit profile of active doses of MDMA, it appears favorable to continue the research of MDMA as an adjunct to psychotherapy.

Based on clinical experience with PTSD, MAPS is exploring new indications for this treatment. Studies for additional indications include one Phase 2 study (MAA-1) of MDMA-assisted therapy for social anxiety in people on the autism spectrum and one study of MDMA-assisted psychotherapy to address anxiety associated with a life-threatening illness (MDA-1). In addition, there is one ongoing Phase 1 study of MDMA-assisted psychotherapy to assess psychological effects in healthy volunteers (MT-1). When completed, this will be the first Phase 1 investigation to assess acute effects in a therapeutic setting that is comparable to MDMA-assisted psychotherapy studies for PTSD.

This IB will present preclinical and clinical studies of MDMA, as well as epidemiological studies in Ecstasy users.

3.0 Physical, Chemical, and Pharmaceutical Properties and Formulation

MDMA is structurally similar, but functionally distinct, from amphetamines and mescaline. MDMA, also known as 3,4-methylenedioxy-N-methylamphetamine and N-methyl-3,4-methylenedioxyamphetamine, has the chemical formula of $C_{11}H_{15}NO_2$. It was first synthesized as a precursor of a haemostatic drug called methylhydrastinine as a phenylisopropylamine derivative of safrole, an aromatic oil found in sassafras, nutmeg, and other plants [56].

MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA, with S(+)-MDMA being more potent than R(-)-MDMA [6, 58]. Research in humans to date and the majority of nonclinical studies have used racemic MDMA, or an admixture containing equal amounts of both enantiomers. Studies of drug discrimination in rodents [94, 95] and studies of self-administered and experimenter-administered MDMA enantiomers in primates [23, 96-99] suggest that MDMA enantiomers may produce different physiological and rewarding effects, and there may be some synergy between the two when administered as a racemate. It seems that R(-)-MDMA may have hallucinogen-like effects, compared to S(+)-MDMA, which exhibits psychomotor stimulant-like effects. Findings comparing the effects of the enantiomers of the related compound methylenedioxyethylamphetamine (MDE) suggest that these different effects of MDMA enantiomers may occur in humans [100]. According to an *in vivo* microdialysis study in rodents, S(+)-MDMA may be associated with greater dopamine release in specific brain areas [101]. A study conducted in 2014 in monkeys found that S(+)-MDMA, but not R(-)-MDMA, significantly increased extracellular dopamine levels in the dorsal striatum, whereas S(+)-MDMA significantly increased serotonin levels [23]. In vitro studies reported greater binding at a specific alpha nicotinic acetylcholine (Ach) receptor by R-MDMA compared with S-MDMA [102]. MDMA available for humans in clinical trials is racemic, containing roughly equal amounts of both enantiomers. Any differential effects of the enantiomers remain untested in humans. The sponsor will use racemic MDMA in all current and planned studies. Unless otherwise stated, MDMA is used throughout this document to refer to the racemic mixture.

For clinical trials, the sponsor used racemic hydrochloride salt of MDMA from two sources. Since this is the formulation used in all prior investigations in humans, the sponsor will continue to use the hydrochloride salt of MDMA. The hydrochloride salt of MDMA is readily water soluble with a pK_a of 9.9 [103], which influences whether it is ionized in plasma and slightly reduces its ability to cross into oral fluid. MDMA is also more lipophilic, which drives it into oral fluid, and may influence its ability to pass the blood brain barrier and influence signaling in the central nervous system (CNS) [104].

Sponsor-supported studies in the U.S. use MDMA manufactured in 1985 by David Nichols, Ph.D., at the Department of Medicinal Chemistry and Pharmacology, Purdue University, West Lafayette, IN. The MDMA was manufactured as a single lot for use in federally approved clinical research. A stability analysis conducted in 2006 indicates that the compound remains highly stable and pure after 21 years of storage [105]. Studies conducted outside of the U.S. use MDMA from a single batch manufactured in 1998 by Lipomed AG in Arlesheim, Switzerland. The most recent analysis of drug stability and purity conducted on February 2, 2010 confirmed that this MDMA is 99.9% pure with no detectable decomposition. For sponsor-supported studies, MDMA in the form of white crystalline powder is compounded with inert material into capsules. Capsules are administered orally with a glass of water.

The sponsor has contracted with Shasun, a manufacturer in the United Kingdom, to manufacture active pharmaceutical ingredients (APIs) to produce 1 kg of MDMA following current Good

Manufacturing Practices (cGMP). The material is planned for use in all Phase 3 studies. Details of manufacturing are available from the manufacturer upon request.

MDMA doses in sponsor-supported studies are fixed within a therapeutic dose range, rather than based on body weight, based on epidemiological information and lack of linear dose response with behavioral effects in Phase 1 and sponsor-supported studies [7]. A typical active dose is 125 mg, which is equivalent to 2 mg/kg for the initial dose. The optional supplemental dose of 62.5 mg is equivalent to 1 mg/kg, for a cumulative dose of 3 mg/kg. Various comparator and active doses of MDMA are also being tested in the clinical trials.

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

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

4.0 Nonclinical Studies

Findings from nonclinical animal research, retrospective studies of Ecstasy use and case reports of Ecstasy use in humans are presented. Research into the pharmacological, physiological, or psychological effects of MDMA began in the 1950s, when the U.S. Army administered MDMA to guinea pigs, monkeys, mice, rats, and dogs as part of a military research program, possibly intending to develop chemical incapacitants or means of enhancing interrogation [106]. Investigations of the pharmacology, functional effects, and toxicity of MDMA in animals have generally included injections of large and often repeated doses of MDMA that are not human-equivalent doses. Studies of MDMA have been conducted in primates and rodents. Primate species studied include baboon, macaque, rhesus monkey, and squirrel monkey, and rodents include mice and rats. Studies of circadian rhythm have occurred in hamsters. Beginning in the mid-2000s onwards, reports re-examining these effects have questioned the applicability of interspecies scaling models for MDMA, and have supported nonlinear pharmacology [78, 107, 108]. In general, doses in the range of 1 to 5 mg/kg in animals are relevant to human research and are described in more detail in Section 4.2.2 Pharmacodynamics in Animals. Findings in doses above this that show a toxic effect are described when relevant in Section 4.4 Toxicology in Animals and Epidemiological Settings.

Evidence exists for intentional human use of MDMA, known as Ecstasy among other names, as early as the late 1960s [57], and there are records of a police seizure of MDMA in the early 1970s [109]. MDMA was administered to thousands of people prior to scheduling and many continue to use Ecstasy around the world in various non-medical settings [1-5]. In this IB, "Ecstasy" (or other common names) refers to material assumed to be MDMA used in naturalistic settings (see epidemiology sections), however when used in these uncontrolled settings the drug may not contain only or any MDMA. One of the problems in assessing the effects of Ecstasy in users is determining the purity and identity of the substance. It may contain other substances along with

or instead of MDMA, and when present, the amount of MDMA can vary widely [110-112]. The majority of studies rely on self-reported use and do not attempt to confirm that material used is MDMA. Synthesis of MDMA is relatively simple, and is often produced illegally in laboratories with no quality control, these synthesized tablets also may be cut or mixed with other psychoactive substances. Substances found mixed with MDMA have included amphetamine methamphetamine, dextromethorphan, paramethoxymethamphetamine (PMMA), paramethoxyamphetamine (PMA), cathinones, ketamine, caffeine, and ephedrine. Retrospective studies in Ecstasy users are described in Section 4.3 Physiological Effects in Epidemiological Settings and case reports of morbidity and mortality in Ecstasy users are included in Section 4.5 Serious Reports, Mortality, and Morbidity in Animals and Epidemiological Settings to provide the context of potential safety information of a related compound to MDMA which has extensive use outside of a research setting.

4.1 Nonclinical Pharmacology

MDMA possesses a complex pharmacological profile that is dominated by its effects as a monoamine releaser and reuptake inhibitor. Its prominent effects on serotonin differentiate it from amphetamine and methamphetamine, which primarily act on dopamine and norepinephrine [21, 60]. In the following sections, the pharmacology of MDMA is presented based on nonclinical animal studies and epidemiological studies.

4.2 Pharmacology in Animals

4.2.1 Pharmacokinetics in Animals

MDMA is metabolized via two hepatic pathways. In the major pathway in rats, MDMA is *O*-demethylenated by cytochrome P450 CYP2D1 and 3A2 to form HHMA, which is *O*-methylated to generate HMMA by catechol-O-methyltransferase (COMT). In the minor pathway in rats, MDMA is *N*-demethylated by CYP1A2 and 2D1 to form MDA, which is an active metabolite. MDA is *O*-demethylenated by the same enzymes as MDMA, with subsequent metabolism by COMT. Metabolites of MDMA are excreted in urine as glucuronide and sulfate conjugates. MDMA and metabolites have shorter half-lives in rats than humans at comparable doses based on plasma C_{max} values. Rats tend to form more MDA and glucuronide-conjugated metabolites than humans [113]. As MDMA dose increases above 2.5 mg/kg s.c. or i.p. in rats, a larger percentage of the administered dose is shunted to the *N*-demethylation pathway, resulting in greatly enhanced formation of MDA [114]. Comparison of metabolic pathways between rats and mice given 10 mg/kg intraperitoneal (i.p.) MDMA indicate that 49.1% of MDMA is metabolized through the HMMA pathway in mice versus 72% in rats, and 18.3% of MDMA is metabolized through the MDA pathway in mice versus 28% in rats based on AUC ratios to MDMA. MDMA at 10 mg/kg was also found to be eliminated more rapidly in mice (0.4 hours, i.p.) than rats at (1.1 hours, subcutaneous (s.c.)) [78, 115].

To address questions of the applicability of interspecies scaling models and nonlinear pharmacology of MDMA, a study examining MDMA and metabolites in rats given 2.5, 5, and 10 mg/kg s.c. found that MDMA metabolism is nonlinear in rats, with 2.5 mg/kg producing plasma C_{max} levels approximating those seen in humans receiving between 75 and 100 mg [14, 114, 116]. Injections of 2 mg/kg s.c. or i.p. in rats were found to be similar to oral administration of 100 mg MDMA in humans based on plasma MDMA and metabolite concentrations [78]. Based on plasma values, a dose of 3 mg/kg i.p. MDMA administered in mice was comparable to a single oral dose of 100 mg in humans [94]. Studies in rats and mice provide compelling evidence of nonlinear pharmacokinetics, likely due to saturation of metabolic enzymes, determined by greater

than expected AUC values for MDMA and MDA after subsequent MDMA doses, while AUCs for HHMA and HMMA remained lower than expected [114, 115].

Single dose pharmacokinetics of oral 7.4 mg/kg MDMA in squirrel monkeys shows two to three-fold higher plasma MDMA concentrations than humans receiving an oral dose of 100 mg, although allometric interspecies scaling predicts an equivalent dose [107]. A study directly comparing MDMA pharmacokinetics in humans and monkeys found that the two species metabolized MDMA in a similar but not identical manner - MDMA half-life in monkeys was less than half the duration seen in humans (1.1 hours at a dose of 2.8 mg/kg in squirrel monkeys versus 8.4 hours after 1.5 mg/kg in humans). Both monkeys and humans exhibit nonlinear pharmacokinetics [14, 118, 119], and it appears they exhibit similar plasma MDMA levels after receiving the same dose of MDMA [119, 120]. These pharmacokinetic findings suggest that nearly all toxicological and behavioral preclinical studies of MDMA use overestimated doses that exceed human-equivalent doses by 2.7 to 10.7 times, depending on route of administration, due to both simple dose conversion and allometric scaling. As a consequence, it is difficult to interpret the relevance of findings in preclinical studies employing these dosing regimes.

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

	C_{max} (ng/ml)	AUC (h•ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	References
Rat [A]					
2 mg/kg i.p.	210±108	163±56	0.14±0.08	0.80±0.16	[78]
2 mg/kg s.c.	196±50	304±65	0.75±0.29	0.79±0.14	[78]
2 mg/kg p.o.	46±15	61±42	0.56±0.31	0.77±0.11	[78]
2.5 mg/kg s.c.	164.1±47.1	272.1±71.6	0.6±0.2	1.1±0.9	[114]
5 mg/kg s.c.	370.8±41	879.1±133.2	0.9±0.6	0.9±0.1	[114]
10 mg/kg s.c.	893.9±90.7	2879.9±491.5	1.1±0.4	2±0.6	[114]
Mouse [B]					
3 mg/kg i.p.[C]	369.8	---	0.17	0.6	[94]
10 mg/kg i.p.	1109±87	1233±53	≤0.3	0.4	[115]
20 mg/kg i.p.	2152±82	2611±86	≤0.3	0.6	[115]
Squirrel Monkey					
1.4 mg/kg p.o.	100.2±51.5	340.3±248.4	1±0.4	1.8±0.9	[121]
2.8 mg/kg p.o.	312.7±92.8	1314.2±581.5	1.1±0.4	2.1±0.8	[121]
5.7 mg/kg p.o.	723.6±228	3866.2±891	1.3±0.9	2.6±0.7	[121]
10 mg/kg p.o.	1594.5±295.6	12,839.2±2144.6	1.3±0.9	4.2±1.5	[121]
7.4 mg/kg s.c.	1227±167	5006±528	---	3.5±0.9	[107]
7.4 mg/kg p.o.	773±157	3408±821	---	3.1±0.5	[107]
Human					
1.0 mg/kg p.o.	147±10	1389±119	2.3±0.2	7.2±0.6	[122]
1.6 mg/kg p.o.	292±76	3485±760	2.4±0.6	8.1±2.1	[116]
1.6 mg/kg p.o.	254.7±60.4	3070.6±673.4	2.4±0.6	8.4±1.6	[119]
2.0 mg/kg p.o.	442-487	5133-5232	1.5-2.0	6.9-7.2	[14]

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

4.2.2 Pharmacodynamics in Animals

Most effects of MDMA likely arise directly from monoamine reuptake inhibition and release, and indirectly from activation of downstream monoamine receptors and subsequent secretion of

neuromodulators oxytocin and AVP. MDMA binds primarily to membrane-bound monoamine transporters, which remove monoaminergic neurotransmitters from the space between neurons, known as the synaptic cleft. MDMA appears to alter the conformation of the transporters, enabling monoamines to diffuse out of the neuron rather than being actively transported into the presynaptic neuron [60, 123, 124]. MDMA prevents the reuptake of serotonin, and to a lesser extent, norepinephrine and dopamine, and facilitates release of these neurotransmitters [60, 125-127]. The selectivity of MDMA for specific monoaminergic neurotransmitters is species-dependent, and cannot solely be attributed to differences in binding affinity for specific reuptake transporters observed *in vitro,* as described below. In *in vitro* studies, MDMA was also found to compete with monoamines for sites on the vesicular monoamine transporter-2 (VMAT2), suggesting MDMA also promotes active release of monoamines from vesicular stores, in addition to inhibiting reuptake [128-130].

MDMA can inhibit monoamine oxidase A (MAO-A) *in vitro* at high concentrations, which preferentially degrades serotonin, and leads to accumulation of extracellular serotonin in the synaptic cleft [131, 132]. Inhibition of MAO-A may have played a role in fatalities and medical emergencies seen after combining Ecstasy with MAO inhibitors in epidemiological settings [133, 134]. Spurred on by prior reports hypothesizing that apparent greater serotonergic toxicity of MDMA in primates, as compared to rodents, could be attributed to greater SERT affinity [135], researchers specifically examined affinity in cells transfected to express human monoamine transporters [127, 136]. These studies found that even though binding affinity of MDMA for the human norepinephrine transporter (NET) exceeded the affinity for SERT and dopamine transporters (DAT), serotonin was preferentially released over norepinephrine and dopamine [127], which may account for primarily serotonergic effects of MDMA. On the other hand, in rodents MDMA affinities for transporters are ordered as SERT>NET>DAT [137]. MDMA does not have as strong an affinity for the DAT as methamphetamine [21].

The ability of MDMA to stimulate release of pre-synaptic serotonin, norepinephrine, and dopamine in multiple brain regions and inhibit reuptake has been well documented [138]. *In vivo* microdialysis and voltammetry results show significant enhancement of serotonin, and to a lesser extent dopamine following MDMA administration, a response attenuated by various transporter inhibitors. MDMA-stimulated serotonin and dopamine release has been measured in the striatum, nucleus accumbens, PFC, and the hippocampus of freely moving rats [139-142]. In addition, enhancement of Ach release has been demonstrated in the PFC, striatum, and hippocampus by both a dopaminergic and serotonergic dependent mechanism [143, 144]. The subjective and physiological effects of MDMA are produced by the dynamic interaction of these transmitter systems on numerous brain networks that modulate learning and memory, emotion, reward, attention, sympathetic/parasympathetic activity, and neuroplasticity.

In addition to carrier-mediated monoamine release, MDMA has affinity *in vitro* for specific serotonin, norepinephrine, Ach, and histamine receptors, although the concentrations tested may not translate to standard human MDMA doses [24, 145-147]. An *in vitro* binding study comparing MDMA with a number of drugs that include cathinone derivatives suggests that contrary to an earlier report of low affinity for $5HT_{2A}$ serotonin receptors, MDMA may have significant effects at the receptor [25]. MDMA likely modulates $5HT_{1A}$ serotonin receptors indirectly through serotonin release, though it is possible that MDMA may also act as a partial $5HT_{1A}$ agonist in some brain areas [148]. Findings from other studies suggest that MDMA shares qualities with $5HT_{1A}$ agonists. Early studies in rats suggest that pharmacological activation of $5HT_{1A}$ receptors reduce anxiety and aggression [149, 150], and some drug discrimination studies suggest that the $5HT_{1A}$ agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) partially or fully substitutes for MDMA [151-153]. In addition to its primary effects, both enantiomers of MDMA enhance Ach release in the PFC [144, 154] and promote changes in GABA-ergic systems

that correlate with sociability [155]. At least some direct or indirect effects of MDMA on serotonin receptors may alter GABA uptake in the ventral tegmental area of rats [156]. An *in vitro* study found that S-MDMA showed signs of competitive interaction with the alpha-4 beta-2 nicotinic receptor which are implicated in learning [157], while R-MDMA did not produce this effect [102].

Infusion of serotonin in the rat brain stimulates secretion of oxytocin into peripheral blood via activation of $5HT_{1A}$, $5HT_{2C}$, and $5HT_4$ receptor subtypes, as well as AVP secretion via activation of $5HT_{2C}$, $5HT_4$, and $5HT_7$ receptor subtypes [158]. MDMA was shown to increase oxytocin and AVP secretion in rats [159] through a $5HT_{1A}$ mechanism [160]. Administering a $5HT_{1A}$ antagonist attenuates the prosocial behavior of rats, measured by preference to lie adjacent to each other, possibly because it prevents elevation in oxytocin [160, 161]. MDMA also promotes norepinephrine release through reuptake inhibition, which is an additional pathway that can contribute to oxytocin secretion and may control emotion regulation. Both oxytocin and AVP are implicated in the widespread regulation of behavioral aspects of mood and also act on different target organs to modulate physiological functions in the periphery [162]. Taken together, MDMA has been shown to have a diverse array of pharmacodynamic effects in animals, with findings of interest presented below by topic.

4.2.2.1 Stable Effects on Gene Expression in Animals

Epigenetic modifications, including deoxyribonucleic acid (DNA) methylation, demethylation, and histone acetylation, are thought to be involved in dynamic regulation of memory reconsolidation in the adult nervous system and play a role in memory formation [163]. Early childhood adversity and trauma is associated with transcriptional silencing of the brain-derived neurotrophic factor (BDNF) gene through DNA methylation, which can either be a risk factor in development of PTSD or a result of having PTSD in adulthood [164]. In a 2015 report, MDMA showed DNA hypermethylation and hypomethylation activity in cardiac tissue by microarray analysis in mice [165], and this activity may extend the CNS. Epigenetic effects on BDNF and other gene expression is a hypothesized mechanism by which MDMA in combination with training in animal studies modeling anxiety disorders, or psychotherapy in humans, exerts its therapeutic effects.

A number of research teams have studied the effects of MDMA on gene expression in rodents [166-169]. However, many of these reports used 10 to 20 mg/kg MDMA, a dose range that is 5 to 10.7 times greater than the 1.5 to 2 mg/kg doses employed in human trials, making it less likely that these changes can be generalized to humans given lower doses. However, even at these doses toxicity was not observed, and a self-administration study at clinically relevant doses reproduced findings of elevation of genes such as serum/glucocorticoid kinase 1 and 3 (*Sgk1, Sgk3*), which regulate glutamatergic signaling and are associated with neuroplasticity and learning, as well as processes involved in memory consolidation in serotonergic neurons [170]. These studies also report an increase in expression of genes that regulate the GABA transporter [166], which is expressed in GABA-ergic neurons indirectly regulated by glutamatergic afferent neurons. Serotonin-transporter knockout mice did not display some of these changes in gene transcription, suggesting that serotonin release is required for this activity [166]. In the acute period 24 to 48 hours after MDMA exposure, a study in rats found 33 to 70% upregulation of BDNF messenger ribonucleic acid (mRNA) transcripts in the frontal cortex, with a time-dependent decrease, up to 73%, of BDNF transcripts in the hippocampus [171]. The frontal cortex and hippocampus are both regions known to play a causal role in memory retrieval and reconsolidation in animals and humans [172], mediated in part through GABA-ergic signaling [173], suggesting that these transcriptional changes may be functionally related.

Examining rat brains after repeated MDMA administration for 2 weeks detected a sharp drop in SERT expression [174], suggesting a compensatory downregulation in response to repeated high doses of MDMA. A study in rats found repeated administration of MDMA at 1 or 5 mg/kg weekly for 4 weeks increased transcripts for $5HT_{1B}$ receptors in various brain regions and $5HT_{2C}$ receptors in the cortex and hypothalamus, likely due to serotonin depletion and subsequent need to increase serotonin receptor availability [175]. Increased levels of gene transcripts regulating extracellular signaling in mice were also reported after MDMA [176]. Serotonin may play a more significant role than dopamine in transcription changes mediated by MDMA [175]. Mouse brains examined 8 hours after 8 days of self-administration or non-contingent administration detected increased transcription of genes related to inflammation and immune modulation in both groups and transcription of genes related to neuroadaptation in mice self-administering MDMA [170]. Transcripts in these studies were assessed 8 to 10 hours after the last of repeated MDMA administrations and it is unclear whether these changes reflect residual acute effects of the MDMA or changes related to repeated MDMA administration. In addition, changes in transcription do not always correlate with functional consequences in proteins levels. BDNF has been shown to have multiple functionally distinct splice variants which have tight temporal and spatial control in an activity-dependent, stimulus-specific manner [177]. However, MDMA produces a durable enhancement of fear extinction in mice, an effect mediated by an MDMA-associated increase in BDNF expression specifically in the context of fear extinction training, suggesting that gene expression changes after MDMA are functionally relevant [178].

4.2.2.2 Immunological Effects in Animals

MDMA acts as a mild immunosuppressant in rodents. MDMA administration at 5 mg/kg in rats is associated with impaired macrophage activity as evidenced by inhibition of Tumor Necrosis Factor-alpha (TNF-α) secretion for 12 hours post-drug [179]. In mice injected with 10 mg/kg MDMA for 5 days, increases in in epithelial tissue of cytokines interleukin 1-alpha (IL-1α), granulocyte-colony stimulating factor (G-CSF), and interleukin 3 (IL-3) were found, while decreased serum levels of many cytokines were reported [180]. MDMA decreased neutrophil oxidative bursts and phagocytosis, and increased the number of circulating neutrophils while decreasing the number of lymphocytes. MDMA also increased hypothalamus-pituitary-adrenal (HPA) axis activity through a noradrenergic pathway in the hypothalamus [181]. MDMA also suppresses interferon-γ secretion and signaling in mice [182]. Interestingly, MDMA was shown to reduce inflammation and airway reactivity in a mouse model of allergic asthma, suggesting that MDMA could have beneficial immunomodulatory effects in cases of heightened inflammation [183]. This constellation of findings was in the 10 mg/kg dose range, which calls to question the applicability to moderate dosing regimens. However, a microarray study found that mice self-administering MDMA at moderate doses had transcriptional changes in many genes related to immune and inflammatory responses as well as neuroplasticity and learning [170], suggesting that immunosuppressant effects of MDMA at clinically relevant doses could be beneficial in the treatment of psychoneuroimmunological disorders such as PTSD [184].

4.2.2.3 Thermoregulatory Effects in Animals

Rodents have generally been used to study the hyperthermic effects of MDMA. Rodents have a much smaller body mass and do not perspire, but use their tail to regulate body temperature which has a large surface to volume ratio, and is perfused with many blood vessels for thermoregulation. Since thermoregulation is different in rodents and humans [185], findings may have limited applicability to humans. MDMA doses that are moderate to high elevate body temperature and disrupt thermoregulation in mice [124], and doses of MDMA in the 1 to 2 mg/kg range only cause a slight increase in body temperature [186]. Rats given doses of 10 mg/kg MDMA (s.c. and i.p.), but not 2 mg/kg, experienced increases in body temperature correlated

with levels of the active metabolite MDA [78, 114]. A study of rats receiving subcutaneous injections of 1 and 3 mg/kg MDMA demonstrated minimal effect on brain hyperthermia using thermal couplers installed in the nucleus accumbens, however ambient temperatures of 29°C and social interaction had a potentiating effect on body temperature and malignant hyperthermia at higher doses [187], described in Section 4.4 Toxicology in Animals and Epidemiological Settings. MDMA effects on body temperature are susceptible to changes in ambient temperature in rodents, with high ambient temperature significantly increasing body temperature in mice and rats, and low ambient temperatures reducing it [188-190]. The MDMA-induced impairment in thermoregulation is caused, at least in part, by peripheral vasoconstriction in the tail, an effect mediated by brain neurotransmitter activity [191, 192].

High doses of MDMA also produce significant elevations in body temperature in primates [107, 193, 194]. At doses closer to those humans ingest [195], monkeys exhibit only slight to moderate elevation in body temperature [196, 197]. In contrast to findings in rodents, primates are not susceptible to changes in ambient temperature when given MDMA, exhibiting slight to moderate increases in body temperature regardless of the temperature of the environment [195-197], though at least one study found that the ambient temperature influenced the effects of 1.5 mg/kg i.v. MDMA on body temperature in monkeys, with lower body temperatures seen after MDMA administered in cool temperatures and higher body temperatures in another group given MDMA at warm temperatures [198]. Findings in rodents do not extrapolate well to primates in this area. Given that the thermoregulatory effects in rodents are highly dose-dependent, the majority of physiological effects seen after low to moderate MDMA administration suggest that a controlled environment and moderate doses would be sufficient to mediate physiological complications associated with hyperthermia, including cardiovascular, osmoregulatory, neurological, and immunological effects.

4.2.2.4 Cardiovascular Effects in Animals

In vivo assessments of cardiovascular effects of MDMA in animals detected increased sympathomimetic activity, as seen in humans [124, 199]. An injection of 2 mg/kg MDMA elevated heart rate in rabbits [633]. Ten mg/kg MDMA produced a relatively larger increase in heart rate in rats than blood pressure, an effect possibly controlled by beta adrenergic receptors [199]. The researchers found that MDMA has both pressor and depressor effects, acting through adrenergic receptors [201-203]. Another study in rodents also suggests that norepinephrine may play a role in cardiovascular effects [204], findings that have been more intensively investigated in humans [205-208]. Given the affinity of MDMA for the NET, it is possible that the cardiovascular effects of MDMA could be attributed to norepinephrine signaling in the peripheral nervous system.

4.2.2.5 Osmoregulatory Effects in Animals

AVP is a key regulator of water balance in the body, and has antidiuretic actions when acting at its V2 receptor subtype in the kidneys [209, 210]. MDMA can influence water regulation by activation of the AVP system, as shown in several animal studies. A study of isolated *in vitro* rat hypothalamus initially reported AVP and oxytocin release after MDMA and its metabolite HMMA [33]. *In vivo* drug-discrimination studies in rats suggest that AVP receptors are involved in producing interoceptive effects of MDMA [162]. When 10 mg/kg i.p. MDMA was administered at 30°C ambient temperature to male Wistar rats, MDMA induced expression of Fos, a marker of neural activation, in the supraoptic nucleus, a brain region important for osmoregulation and a key mediator of oxytocin and AVP release [211]. This finding suggests that MDMA can have osmoregulatory effects in rats at high doses administered at warm ambient temperatures.

4.2.2.6 Neurobiological Effects in Animals

It appears that single doses of MDMA (2.5 mg/kg i.p. in monkeys, 7.5 mg/kg i.p. in rats), approximately four times a human equivalent dose, reduces brain serotonin production for 2 weeks or more [107] but does not increase validated markers of neurotoxicity associated with neurodegeneration [108]. Monkeys allowed to self-administer MDMA for an 18-month period had no reductions in brain dopamine, slight reductions in brain serotonin, and no chemical markers of neuronal injury [509]. One report detected a reduction in N-acetylaspartate to creatine ratio, which the authors considered a sign of neuronal injury, although no decreases in brain serotonin were detected after administration of two human-equivalent doses of MDMA to marmoset monkeys for 2 days [213]. A study examining the rat hippocampus reported indications of apoptosis after 5 or 10 mg/kg given daily for 1 week but not after 2.5 mg/kg [214]. Doses of 10 mg/kg administered s.c. and i.p., but not 2 mg/kg, produced signs of serotonin syndrome in rats, but neither dose reduced total serotonin levels in the brain 2 weeks after drug administration. Serotonin syndrome is defined as an excess of serotonin in the CNS causing a suite of specific signs and symptoms that can require intervention [215-217]. Serotonin syndrome severity correlates with MDMA plasma concentrations [78]. Taken together, MDMA doses up to 2.5 mg/kg appear to alter regulation of serotonergic signaling in the rat brain without producing damage to serotonin axons, based on transient reductions in brain serotonin and SERT levels, in the absence of indicators of neuronal injury or decreased expression of the SERT gene [88].
In rats, large doses of MDMA (10 or 20 mg/kg) elevated serum corticosterone (a rodent cortisol analog) and prolactin [218-220], with elevation lasting up to 4 hours after dosing, and with hormone levels attenuated by a $5HT_{2A}$ serotonin receptor antagonist. Given the dosage used was five to 10.7 times larger than an active dose in humans, it is unclear if this response is analogous to elevated cortisol in humans or whether it reflects a different process. Administering 1 to 3 mg/kg doses found that R(-)-MDMA, but not S(+)-MDMA, significantly increased prolactin levels in rhesus monkey plasma, suggesting that at least the R(-) enantiomer of MDMA can influence endocrine signaling at doses relevant for studies in humans [23]. Fluoxetine attenuated prolactin release after administration of racemic MDMA, and fluoxetine and a $5HT_{2A}$ antagonist attenuated prolactin release after R(-)-MDMA, indicating that prolactin release is associated with serotonin release and indirect action on $5HT_{2A}$ receptors by R(-) -MDMA [99].

Serotonergic deficits are associated with disruption of sleep patterns and architecture. In drug-naïve rats, a single dose of 15 mg/kg MDMA i.p. contributed to marked increases in motor activity, deep slow wave sleep, and wakefulness for 5 to 6 hours. Circadian patterns of motor activity and sleep/vigilance parameters were altered for up to 5 days post-treatment, after which most parameters returned to normal. In a single exposure to MDMA 3 weeks prior to the same procedure, rats experienced the same acute effects, but with shorter duration, suggesting that MDMA has the ability to influence sleep architecture and patterns acutely after this dose in drug-naïve rats, but these effects are mediated by experience with MDMA and do not persist beyond 1 week [221].

4.2.2.7 Neuropsychological Effects in Animals

In rodents, doses of MDMA equivalent to human doses produce few behavioral effects. However, several dose-dependent differences on behavioral tests in rats have been reported, including increased locomotor activity and anxiety-related behaviors thought to be associated with serotonin syndrome [161, 222], and decreased social anxiety at 5 mg/kg i.p. [161]. Rats given 7.5 mg/kg MDMA, equivalent to four times the dose tested in humans, exhibited increased anxiety in the elevated plus maze [223], while rats given 15 mg/kg MDMA, equivalent to eight times the

dose tested in humans, exhibited reduced anxiety on the maze. A study of the sub-acute effects of four different doses of MDMA given daily for 1 week, found reduced anxiety with 1.25 and 2.5 mg/kg and increased anxiety with 5 and 10 mg/kg [214]. Lower doses used in these studies are comparable to dose used in human research and nonmedical settings. However, sample sizes used in the study were small. Rats given higher doses also reduced aggressive behavior as well as social investigation. MDMA produces some repetitive behavior in rodents, but not to the same degree as psychostimulants. Rats on MDMA walk around a cage perimeter, interpreted as an indicator of thigmotaxis, which is a sign of anxiety [124]. However, it is notable that a 2007 publication failed to find thigmotaxis in rats given 5 mg/kg MDMA [224]. In contrast, rhesus monkeys do not exhibit increased locomotor activity after receiving up to 2.4 mg/kg MDMA [197]. Some researchers have proposed that behavioral tests of anxiety may instead be measuring risk-taking behavior, or impulsivity [225]. It is also notable that the majority of rat studies with deleterious behavioral findings were conducted specifically in inbred male Wistar rats, suggesting that individual and gender-based differences could influence these findings [226, 227]. Preclinical data in animals suggests that the profile of neurotransmitter release observed after MDMA administration may increase the risk of mania in some individuals [228], although mania has not been a reported as a side effect of MDMA or Ecstasy in humans. Conflicting findings on anxiogenic and anxiolytic dose-dependent effects of MDMA are likely to have limited applicability to humans, with transient anxiety being a possible side effect.

To date, no empirical investigations have been conducted on the effects of MDMA on primate social interactions, which limits the generalizability of rodent studies to the more complex and relevant social behavior of primates and humans. Morley and colleagues observed rat behavior after receiving 5 mg/kg MDMA, noting that this dose correlated with prosocial behavior, such as lying next to each other [161]. Subsequent studies suggest that MDMA increases prosocial behavior in rats by elevating oxytocin in the paraventricular nucleus through $5HT_{1A}$ receptor agonism, with the oxytocin increase arising from the indirect effects of MDMA on $5HT_{1A}$ receptors via serotonin release [160, 229, 230]. There have been no human pharmacological challenge studies combining MDMA with $5HT_{1A}$ agonists, while $5HT_{1A}$ antagonists have negligible effects on subjective or physiological effects of MDMA in humans [92, 231-233]. As a result, it is unclear whether the rat behavior is analogous to human reports of increased feelings of empathy or interpersonal closeness while under the influence of MDMA [2, 13, 234, 235].

MDMA given before training persistently enhances fear extinction learning in mice through a BDNF-dependent mechanism [178], which could be a possible mechanism of action for MDMA in combination with psychotherapy as a treatment for anxiety disorders. The dose of 5.6 mg/kg was approximately two times a human equivalent dose based on plasma values, but the findings are the first biological evidence of a lasting effect of MDMA on disruption of anxiety-related behavior in mice.

4.3 Physiological Effects in Epidemiological Settings

The vast majority of non-clinical epidemiological studies are retrospective comparisons of people who have previously self-administered Ecstasy, a study design that is unable to eliminate the possibility that one or more predisposing factors may lead to repeated Ecstasy use and the variables compared [5, 89, 236]. Samples are often selected on the basis of moderate to heavy self-reported Ecstasy use, with very few studies conducted in samples reporting the levels of moderate exposure seen in clinical trials. Many investigations have compared people reporting use of Ecstasy with non-Ecstasy using controls, mostly as a means of detecting long-term effects of Ecstasy use. Many of the studies do not appropriately match samples for substance use behavior, there is often concurrent use other illicit substances and the Ecstasy used is of unknown purity, dosage, and composition.

The acute effects of MDMA have an initial onset of approximately 30 minutes after oral intake and are characterized by anxiety, tachycardia, and elevated blood pressures [237]. Typical effects include diaphoresis, bruxism, jaw clenching, paresthesias, dry mouth, increased psychomotor activity, and blurred vision. Within an hour, these sympathomimetic effects are replaced by feelings of relaxation, euphoria, increased empathy, and communication. Taking a smaller supplemental dose may prolong these effects and this is being tested in the context of clinical trials. However, when too much additional MDMA is consumed in an uncontrolled setting, individuals report unpleasant symptoms of autonomic hyperarousal associated with feelings of restlessness, paranoia, and anxiety. With increased dosage sympathomimetic effects predominate, placing the patient at risk for cardiovascular instability, arrhythmias, and hyperthermia (see Section 4.4 Toxicology in Animals and Epidemiological Settings).
Retrospective surveys of Ecstasy use offer similar accounts of subjective effects to those reported in controlled studies of MDMA. Study respondents report experiencing stimulant-like effects, such as greater energy or talkativeness, and hallucinogen-like effects, including perceptual changes, visual distortions, or poor concentration, as well as feelings of closeness, compassion, or empathy toward the self or others [2, 234, 235, 238, 239]. The disparity in detection of entactogenic effects in retrospective versus controlled studies is largely due to failure to measure these effects, but might also relate to aspects of setting in controlled studies that do not permit enough unstructured interpersonal contact to produce or facilitate feelings of interpersonal closeness. Starting in the 2010s, more researchers are seeking to assess the prosocial effects of MDMA [35, 37, 38, 240].

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

4.3.1 Immunological Effects

As supported by mild immunosuppressant effects found in rodents, a longitudinal study of regular Ecstasy and cannabis users found a sustained reduction in IL-2, increased levels of Transforming Growth Factor-Beta (TGF-ß), and reduced CD4 cells, and regular Ecstasy and cannabis users reported experiencing a greater number of mild infections than occasional Ecstasy and cannabis users on a structured questionnaire [241]. Immunological effects of MDMA in humans are likely to involve serotonergic pathways and are discussed in more detail in Section 5.3.2 Immunological Effects.

4.3.2 Thermoregulatory Effects

Thermoregulatory effects of Ecstasy taken in epidemiological settings are highly dependent on dose [242] and permissive factors, including high ambient temperature [243, 244], crowded conditions involving overwhelming social interaction, physical exertion, reduced fluid intake [243], and thyroid dysregulation [245, 246]. In the absence of these permissive factors from use in epidemiological settings, hyperthermia is rarely reported. For a detailed discussion on thermoregulatory effects when Ecstasy is combined with permissive factors, see Section 4.4.6 Hyperthermia.

4.3.3 Cardiovascular Effects

Studies in Ecstasy users indicate that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities [247]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Previous to this, echocardiographic readings in eight Ecstasy users also failed to find any cardiac abnormalities [45]. Valvular heart disease (VHD) only occurred after extremely heavy Ecstasy use, it is unlikely to be a risk within the research or therapeutic context where subjects are screened for relevant pre-existing conditions. For more information on toxicological effects, see Section 4.4.7 Cardiovascular Toxicity.

4.3.4 Osmoregulatory Effects

Ecstasy use has been associated in the literature with acute symptomatic hyponatremia with the syndrome of inappropriate antidiuretic-hormone secretion (SIADH) involving raised antidiuretic-hormone, also known as AVP [248]. SIADH refers to disorders related to water and sodium balance characterized by the impairment of urinary dilution and hypotonic hyponatremia in the absence of renal disease or other identifiable non-osmotic stimuli known to activate the release of AVP [249]. MDMA is known to cause central release of both oxytocin and vasopressin through indirect effects of serotonergic signaling as previously described, and this activity indicates that it is not accurate to attribute the osmoregulatory effects of Ecstasy to SIADH, but rather this should be characterized as a pharmacological effect on AVP secretion.

AVP plays a key role in osmoregulation, and is released upon a change in plasma osmolality [250]. AVP is also involved in the response and adaptation to stress, through its effects on the HPA axis [250]. The rise in AVP does not seem to be part of a generalized stress response, but results from a pharmacological effect compounded by excessive fluid ingestion [251]. In Ecstasy users with confirmed urinary MDMA, a significant association was found between plasma osmolality, plasma sodium, and CYP2D6 extensive metabolizer/ intermediate metabolizer genotypes and COMT low-activity genotypes [252]. Effects of Ecstasy, combined with increased consumption of water and permissive factors, such as strenuous exercise in warm ambient temperatures, can be further exacerbated in the context of poor metabolism. Gauging appropriate water intake may be difficult for users to estimate because MDMA reduces perception of thirst and impairs judgment [253]. For more information on the risk of hyponatremia, see Section 4.4.8 Hyponatremia.

4.3.5 Neurobiological Effects

Spurred on by animal studies that found repeated or high doses of MDMA damaged the axons of serotonin neurons, researchers began studying the effects of repeated non-medical or recreational use of Ecstasy in humans [83-85, 254]. Early investigations had a number of methodological flaws, including retrospective design and poor matching of Ecstasy users with appropriate controls [89, 255]. Later studies sought to remedy some of these problems by using carefully matched polydrug user or cannabis user controls, or by relying on a sample with relatively low exposure to psychoactive substances, including alcohol [256-259]. Some of these investigators also conducted longitudinal studies, comparing Ecstasy users, sometimes alongside controls, at two separate time points [260-262].

Researchers using slightly different methods have reported differing results. These include finding no differences between Ecstasy user and polydrug user controls in SERT binding sites [263], modest reductions in estimated SERT sites in Ecstasy users versus non-drug using or cannabis-using controls [264], and an association between decreased SERT sites and lifetime

Ecstasy use [265]. This study also reported finding slightly fewer $5HT_{2A}$ receptor binding sites in both "Ecstasy preferring" and "hallucinogen preferring" groups. Studies in low to moderate Ecstasy users did not report an increase in this marker [266], and only one of three studies in heavy users detected a change in $5HT_{2A}$ receptor density. [267-269]. A prospective study in moderate Ecstasy users also failed to find any chemical markers of neuronal injury, and only found decreased cerebral blood volume in the dorsolateral frontal cortex [266, 270]. A re-examination of brain imaging using the less specific SERT marker Beta-CIT indicate an inverse relationship between age of first use of Ecstasy and mid-number of midbrain serotonin sites without detecting any relationship between age of first use and frontal SERT sites [271]. A retrospective imaging study using a radioligand that maps serotonin synthesis found lower ligand presence ("trapping") in prefrontal, orbitofrontal and parietal areas and higher presence in brainstem, frontal and temporal areas in Ecstasy users versus polydrug user controls, with a greater difference seen in men [272]. The researchers reported relationships between differences in trapping and cumulative use, duration and temporal proximity of use. The samples were not well-matched for drug use.

Studies comparing brain activity in Ecstasy users and non-Ecstasy using controls reported some but not many differences in brain activity. These included greater brain activation in the occipital cortex, with concomitant methamphetamine use contributing to increased activation to a visual stimulus [273]. The same group of researchers detected less within-region coherence in the thalamus in Ecstasy users who averaged 29 episodes of use when compared with non-Ecstasy-using controls [274]. In a retrospective study, Ecstasy users exhibited lower brain activity in bilateral dorsolateral prefrontal cortex compared with controls reporting no illicit drug use, with neither group exhibiting impaired task performance [275]. Ecstasy users exhibited a single difference in brain activity compared to polydrug using controls. A prospective study comparing brain activity before and after use of Ecstasy failed to detect differences in working memory, attention or brain activity [276], suggesting a relationship between repeated, regular use of Ecstasy and other drugs and changes in brain activation. Investigations of the interaction between genotype and regular Ecstasy use have supported differential effects upon reward-based attention or visual or verbal memory [277-279], with some findings supporting differences due to genotype and some failing to do so. A systematic examination of imaging studies comparing ecstasy users reporting consumption of 100 or fewer tablets with controls reported finding no evidence for an association between moderate Ecstasy and signs of structural or functional changes in the brain [79]. Given the small samples and uneven numbers with different genotypes, any conclusions await further support.

Sleep disturbances are thought to be associated with deficiencies in serotonergic signaling [280]. Examining sleep architecture in Ecstasy users, investigators found less total sleep time and less stage 3 and 4 sleep on the adaptation night, but no overall differences in sleep architecture [281]. Another study comparing heavy Ecstasy users with non-drug using controls found no differences in baseline sleep using electroencephalography (EEG) [282]. Early studies in mostly heavy Ecstasy users reported significant decreases in total sleep as well as stage 2 sleep [283], while studies conducted in the 2000s found Ecstasy users were able to fall asleep more easily upon depletion of catecholamine neurotransmitters suggesting an underlying difference in serotonergic control of sleep architecture [284, 285]. Findings of sleep disruption in Ecstasy users are not likely to be applicable to the exposures seen in research or therapeutic settings.

A study of breathing during sleep in 71 Ecstasy users and 62 polydrug users did not find overall differences in disrupted breathing, assessed via nasal cannula, but found that all moderate and severe breathing disruptions occurred in the Ecstasy using sample [286]. McCann and colleagues reported a relationship between cumulative (lifetime) Ecstasy exposures and instances of disrupted breathing during non-REM sleep and suggested Ecstasy users could be vulnerable to

potentially fatal sleep apnea. In contrast, other researchers failed to find greater night-time awakenings indicative of sleep apnea in Ecstasy users [281, 282], and the high rate of disrupted breathing McCann and colleagues detected even in the controls suggest that this measure may not provide clinically significant assessments. Taken together, it appears that MDMA acutely produces lighter sleep with fewer REM periods.

4.3.6 Neuropsychological Effects

Previous reports have found an association between Ecstasy use and symptoms of depression or anxiety [287, 288]. A meta-analysis of self-reported depressive symptoms detected an association between Ecstasy use and scores on the Beck Depression Inventory (BDI), a popular self-report measure of depression symptoms [289]. However, the association was strongest in studies with small samples, and drug use variables were often incompletely reported and not verified through any methods save self-report in the studies analyzed. Many studies found that increases in self-reported anxiety or depression were more strongly related to polydrug use rather than to use of any one substance [290-293]. Two studies found an equal or stronger association between regular use of cannabis, and not Ecstasy, with anxiety, depression or other psychological problems [294, 295]. Anxiety regarding loss of control under the influence of Ecstasy could develop to a degree where it could lead to panic attacks. Case reports have been published describing panic attacks in individuals under the acute influence of Ecstasy [296]. Enduring panic attacks have been reported in individuals after repeated Ecstasy use [297, 298] and in one case, even after a single dose [299].

Neuroendocrine response to oral citalopram did not differ between Ecstasy users, cannabis users and controls [300]. People reporting regular drug use and Ecstasy use had higher levels of salivary cortisol in the evening, and higher salivary cortisol on the day of a multitasking activity [301], and higher salivary cortisol on waking that was unrelated to prefrontal SERT binding or self-reported depression symptoms [302]. A 4-year longitudinal study reported that factors other than Ecstasy use, including female gender and presence of financial and relationship difficulties, were more closely related to self-reported symptoms of depression [303]. Comparison of self-reported psychological symptoms in samples of people grouped by self-reported drug use found current Ecstasy users had lower global symptom severity scores than polydrug users [304]. In conclusion, it appears that the relationship between Ecstasy use on self-reported mood or psychiatric problems is not strong, with equal or stronger involvement of other factors.

In a prospective study comparing cognitive function in people before and up to 18 months after reported initiation of Ecstasy use, Schilt and colleagues found an association between Ecstasy use and performance on measures of verbal memory, but not attention or working memory [305]. All scores were within normal range; people who did not use Ecstasy showed greater improvement in performance at the second time of assessment than people reporting some use. A second prospective study examined working memory in people reporting Ecstasy use similar to subjects in Schilt's study with controls, and failed to find any significant differences in working memory and selective attention [276]. An analysis of findings from largely retrospective studies of Ecstasy users reported a small deficit in verbal or working memory [53]. Retrospective studies of polydrug users who use Ecstasy and controls reported impaired global motion processing without changes to local processing [306].

Not all studies report that Ecstasy users fare worse on measures of cognitive function than controls. A number of reports detected little or no significant differences between Ecstasy users and polydrug user controls in performance on tasks of cognitive function [236, 275, 276, 307-311], though other studies continue to find consistent differences, particularly in verbal memory [285, 312-315]. Regular use of many substances, including alcohol, may affect cognitive

function, with Ecstasy being only one of those substances [316]. Several reports have found relationships between cognitive function and use of other drugs as well as or instead of Ecstasy [278, 307, 309, 312, 317, 318].

The only study attempting to address effects of Ecstasy use on cognitive function in middle aged versus younger users did not find a greater degree of impairment. Schilt and colleagues reported impaired verbal memory in people who began using Ecstasy in their 30s compared with age-matched drug-naïve and polydrug using controls reporting some lifetime Ecstasy use, but did not find a greater effect size for Ecstasy use in this sample than in samples of younger Ecstasy users, leading them to conclude that Ecstasy use does not have a greater impact on cognitive function in older users [319].

The relationship between Ecstasy use and impulsivity has also been extensively examined, with some researchers reporting greater impulsivity in Ecstasy users and others failing to find any differences [84, 320]. Recent studies using both behavioral and self-report measures of impulsivity reached contradictory conclusions [311, 321, 322]. Two recent studies using the same measure of behavioral impulsivity in samples of heavy Ecstasy users obtained different findings [311, 321]. It is notable that Quednow and colleagues compared Ecstasy users with abstinent cannabis users and drug-naïve controls while Roiser and colleagues compared Ecstasy users with former Ecstasy users, polydrug users and drug-naïve controls, raising the possibility that results might have differed in part due to control group selection. It is possible that people who self-administer Ecstasy may already possess above-average levels of sensation-seeking and impulsiveness. To date, all such studies have used retrospective study designs and cannot rule out this possibility, and studies published in the last 2 years suggest that polydrug use may be equally or more strongly related to impulsivity in Ecstasy users [323-325]. The relationship between drug use, including Ecstasy use, and impulsivity, is complex.

4.4 Toxicology in Animals and Epidemiological Settings

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

4.4.1 Single Dose Studies in Animals

Single doses between 5 and 60 mg/kg have been administered in rodents. Since rodents are similar to primates in mg/kg dosing, the doses of 5 mg/kg and above, administered by any route of administration in rodents, are inappropriately high for comparison to human studies utilizing doses less than or equal to 125 mg, so findings are only useful as models of toxicology or abusive use in humans. A study of the long-term effects of a single dose of 5.7 mg/kg MDMA on estimated SERT sites in the brains of squirrel monkeys reported reduced sites in some frontal, temporal and parietal areas [326]. The plasma C_{max} of 725 µg/L in squirrel monkeys was three times greater than what is observed in humans after a single dose of 100 mg MDMA (C_{max} of 202.92 to 222.5 µg/L) [113, 327, 328], even after administration of a supplemental dose twice that of the initial dose 2 hours later, which increased C_{max} to 311.16 µg/L [328]. A handful of studies in rats have examined the effects of single toxic doses in comparison to low doses and determined that single doses have transient effects on serotonin depletion [78, 114, 108], likely due to reversible inhibition of tryptophan hydroxylase [17, 18, 20], which prevents additional serotonin from being produced and released.

4.4.2 Repeated Dose Studies in Animals

The majority of toxicological studies employed multiple dosing regimens to account for the shorter drug half-life in animals compared to humans, with doses ranging from 5 mg/kg to 20 mg/kg, via s.c., i.p., oral, or gavage administration. Frequently, doses are administered at regular intervals of two to four times per day. Other regimens employ these doses once daily for 5 or 7 days. Nearly all preclinical toxicology data is derived from repeated dose studies. Preclinical research selected doses through use of simple dose conversions or allometric scaling, a method of modeling human equivalent doses in other species [329]. Comparison of pharmacokinetic data ($C_{max,}$ AUC, T_{max}) for plasma MDMA concentrations between humans and rodents, in light of the impact of route of administration, it is difficult to translate the relevance of high dose multi-day dosing findings in preclinical toxicity studies to intermittent dosing regimens in humans.

In order to establish the DMF and IND for MDMA, the sponsor supported randomized 28-day general toxicity studies in both genders of the rat (0, 10, 50, 100 mg/kg oral) and the dog (0, 3, 9, 15 mg/kg oral)[330]. Both sexes of dogs on 9 and 15 mg/kg MDMA and rats on 50 and 100 mg/kg MDMA gained less weight than those on control and 3 mg/kg, with significant differences in food consumption observed as early as the first week which were no longer significantly different by the fourth week. Gross observations at necropsy in the dog possibly related to MDMA included reduced testicular size on 9 and 15 mg/kg in the dog and prostatic enlargement in two dogs on 15 mg/kg. No gross lesions were seen in the rats at necropsy. Blood chemistry and urinalysis values were unremarkable in the dog. Clinical pathology findings showing a trend to decrease with dose in the rat were urinary pH, blood urea nitrogen, glucose, creatinine (females), lactate dehydrogenase (females), and chloride, in contrast total white blood cell count (WBC) and phosphorus showed a trend to increase with dose. No MDMA-related lesions were seen in the brains of either species.

4.4.3 Genotoxicity

An Ames test of Ecstasy tablets with 0 to 57.5% MDMA, quantified by GC-MS, found no evidence of genotoxicity [331]. Micronuclear and chromosomal aberrance tests were performed in Chinese hamster ovary cells with MDMA purified from seized Ecstasy tablets and with N-nitroso-MDMA (N-MDMA), a putative metabolite of MDMA [332]. MDMA did not produce increases in either *in vitro* genotoxicity test.

4.4.4 Carcinogenicity

There are no preclinical findings directly addressing the carcinogenicity of MDMA. No tumors were reported after 28 days of daily MDMA administration in rats (0, 10, 50, 100 mg/kg) and dogs (0, 3, 9, 15 mg/kg) in a sponsor-supported preclinical study [330]. In the absence of positive results in genotoxicity tests, carcinogenic potential from intermittent dosing of limited number of exposures to MDMA in controlled settings is not of concern.

4.4.5 Reproductive and Developmental Toxicity

MDMA (15 mg/kg, s.c.) administered to pregnant rats was detected in amniotic fluid [333] indicating the potential for neonatal exposure. Preliminary teratological studies in rats (N=12 per dose) given 0, 2.5, or 10 mg/kg MDMA by gavage on alternate gestational days (GD) 6 to 18 found no abnormalities in gestational duration, litter size, neonatal birth weights, or birth defects (N=10 litters per dose), despite statistically significant reduction in maternal weight gain at 10 mg/kg [334]. These results are in contrast to physiological abnormalities resulting from prenatal methamphetamine and d-amphetamine exposure in mice and rabbits [335].

In a single-generation fertility and developmental toxicity study, C57BL/6 mice (N=25 per dose per gender) received a daily dose of 0, 1.25, 5, or 20 mg/kg MDMA via gavage [336]. Dosing for females spanned 2 weeks before mating through GD15 of pregnancy. Dosing for males spanned 4 weeks through the first day of pregnancy. There were no cases of MDMA-related mortality in females at all treatment levels. Gross necropsy of organs of MDMA-treated groups of male and female mice were unremarkable. No changes in copulation or fertility indices arose in MDMA-treated animals, but fewer pregnancies arose in all three MDMA-treated groups. When the fetuses were examined, no external, visceral, or skeletal malformations were detected in control or 1.25 mg/kg groups, but at 5 mg/kg (2 of 129) and 20 mg/kg (5 of 138) fetuses exhibited a cleft palate, anophthalmia, or skeletal malformations (short tail). Taken together, these studies suggest that MDMA has weak reproductive or developmental toxicity at high doses when MDMA exposure starts 2 weeks prior to mating and continues through GD15, which temporally covers ovulation through organogenesis and closure of the hard palate, in the females and spermatogenesis in the males.

In a separate perinatal/postnatal toxicity study done by the same researchers, C57BL/6 female mice (N=25) received a daily dose of 0, 1.25, 5, or 20 mg/kg MDMA via gavage daily from GD6 slightly after implantation through postnatal day (PND) 21 end of lactation [336]. Pup viability was assessed daily and gross external examination of pups occurred on PND 0, 4, 7, 14, 21, and 28. Behavioral and physical indices of development were observed in the F1 animals, such as pinnae detachment and righting reflex. Testes descent in males occurred on PND20 and vaginal opening occurred in selected females on PND30. Delivery and post-partum (nesting) behavior did not differ across treatment groups, and no MDMA-related differences in pup viability were detected, including pup survival rate and sex ratios per litter. No significant abnormalities were observed at necropsy of mice either found dead at lactation nor killed at PND20. In contrast to the first study described above where MDMA was given 2 weeks before mating through GD15, when MDMA was given to only the females from GD6 to the end of lactation (both studies covered the period of organogenesis and closure of hard palate), there were no signs of impaired development and no significant differences in sexual development or reproductive capacity of F1 and F2 mice. This suggests that either dual exposure of male and female breeding pairs exacerbated reproductive toxicity, or possible evidence of a critical period for MDMA reproductive toxicity prior to organogenesis.

Male fertility after prenatal exposure was studied in male pups born to female Sprague-Dawley rats (N=6 per group) that received 0, 0.5, 5, or 10 mg/kg s.c. daily for three consecutive days per week for 10 weeks, including gestation and 3 weeks of lactation [337]. These females were mated with untreated males. The 5 mg/kg s.c. dose is two-fold greater than a human-equivalent dose based on plasma levels in other studies [78, 114, 119] and s.c dosing leads to higher plasma levels then dosing by gavage which was used in the studies above. There were no signs of toxicity in the 0.5 and 5 mg/kg groups, but dams in the 10 mg/kg group showed signs of sickness the week before delivery, and four of the six receiving 10 mg/kg and one of the five receiving 5 mg/kg were found dead at or prior to GD16. Mortality at 10 mg/kg s.c. indicates that this dose is too high for use in reproductive toxicity studies; the authors subsequently discontinued the 10 mg/kg dose after week 10. Vestibular and motor function were assessed on PND21, with no differences between groups. Balano-preputial separation happened later than controls after 5 mg/kg in male pups on PND37-54. There were no differences in mating or fertility rate in F1 males. Hormone levels were similar across groups at PD81 and sperm morphology was unaffected. However, MDMA administration resulted in a significant higher incidence of DNA damage in Comet Test of sperm DNA at 5 mg/kg in relation to the control group. Minor dose-dependent alterations were seen in testicles, spleen and kidneys. There were no pathologies of the epididymis. Testicles showed a slight decrease in numbers of germ cells in 5 mg/kg treated rats.

A second study investigated male fertility after 0.5, 5 and 10 mg/kg administered s.c. once daily three times per week in rats (N=20 per group) for 12 weeks, covering puberty to onset of sexual maturity [338]. Ten rats per dose were mated with untreated females, with mating behavior alone serving as measure of reproductive function without reporting signs of conception. The other 10 rats per group were examined for testicular and sperm parameters, including sperm count and motility and morphology. There was a dose-dependent increase in tubular degeneration in testes in MDMA-treated rats, but sperm motility and morphology was unaffected. In a sponsor-supported preclinical study, microscopic evidence of possible testicular atrophy and prostatic enlargement was also found in one of three dogs after 28 days of 9 mg/kg oral MDMA and in two of three dogs after 15 mg/kg oral MDMA [330]. Taken together, these studies suggest minimal male fertility toxicity at human-equivalent doses, with signs of increased toxicity at higher doses.

In an initial developmental toxicity study, pregnant rats were administered twice-daily injections of high doses of MDMA (15 mg/kg) or saline from embryonic days (E) 14 to 20. Rat pups that had received MDMA showed reductions in the dopamine metabolite homovanillic acid, along with reductions in the serotonin metabolite 5-HIAA. Prenatally exposed MDMA animals also had reduced dopamine and serotonin turnover in the nucleus accumbens [339]. The same team reported postnatal exposure to MDMA correlated with reductions in serotonin and its metabolite, as well as significant increases in dopamine turnover and the prevalence of a dopamine metabolite in multiple forebrain structures and the brainstem. BDNF was significantly increased (19% to 38%) in all forebrain structures and in the brainstem in MDMA-exposed neonates [340]. The researchers proposed that the increase in BDNF was compensating to minimize MDMA effects. However, later studies found that neonatal MDMA exposure did not affect hippocampal concentrations of serotonin or dopamine [341] and that enhanced BDNF detected in the occipital lobe did not mediate the abnormal serotonergic signaling observed following neonatal MDMA exposure [342]. PND 11 and 20 were proposed to be equivalent to the third trimester of gestation in humans [340], so it is possible that exposure to high doses of MDMA *in utero* could have developmental effects, but these do not appear to be related to BDNF levels. The doses used in the rat studies are approximately eight to 10 times greater than a human equivalent dose.

Prenatal MDMA exposure at high doses significantly increased locomotor activity of rat pups in a 20-minute novel cage environment test [339]. Rodents treated with MDMA during development were not significantly different than rodents who received MDMA as adults. The results of several behavioral tests indicate that developmental MDMA exposure combined with adult exposure may interfere with some aspects of learning, including visual-spatial memory and time spent with a novel object [341]. Neonatal MDMA administration did not alter working memory in the object-recognition test in young adulthood (PD 68 to 73) and there were no differences in binding of the radiolabeled selective serotonin reuptake inhibitors (SSRI) citalopram to the SERT at this age. However, the pretreated animals showed increased thermal dysregulation and serotonin syndrome responses following MDMA challenge, especially with respect to head-weaving stereotypy [343]. Another team also found that neonatal rat MDMA exposure exacerbated hyperthermic response to a subsequent dose to MDMA [344]. A study in neonatal rats suggests two distinct critical periods wherein repeated doses affected learning versus acoustic startle [345]. Serotonergic factors may be involved in the developmental effects of MDMA, with the SSRI citalopram producing similar learning impairments in neonatally exposed rats [346]. Given differences between human and rodent development and thermoregulation, it is not clear whether such findings can be generalized to humans (see Section 4.2.2.3 Thermoregulatory Effects in Animals).

Previous research supported a possible link between Ecstasy use and birth defects [347], while an epidemiological study of a large cohort of pregnant women in England conducted in 2004 failed

to support this link, at least in respect to a specific cardiac defect [348]. However, the authors also stated that exposure to MDMA in their sample was too low to establish risk. An earlier survey of a drug-using population suggests that most women cease using Ecstasy when they learn they are pregnant [349]. A 2012 survey of 96 women in the UK interviewed about their drug use during pregnancy found a link between self-reported extent of prenatal MDMA exposure and delays in infant development at 12 months, with heavily exposed infants delayed in mental and motor development, but not language or emotional development [350]. These results were repeated in a 2016 survey of 96 mothers who reported heavier MDMA use (1.3±1.4 tablets per week) during pregnancy. Infants had motor delays from 4 months to 2 years of age that were not attributable to other drug or lifestyle factors [351]. Since there may be a critical period during which exposure to MDMA could alter development, and as a result of the relative lack of information concerning its developmental toxicity, women who are pregnant or who are not using an effective means of birth control should not receive MDMA in clinical trials. None of the sponsor's studies enroll pregnant or lactating subjects.

4.4.6 Hyperthermia

At least one case series of individuals seen on the same night and near or in the same nightclub suggest a relationship between Ecstasy dose and likelihood of hyperthermia [352]. A case report and some findings in rodents suggest that hyperthyroidism or thyroid dysregulation may play a role in MDMA-related hyperthermia in humans [245, 246]. When assessing acute effects of Ecstasy, hyperthermia is one of the more frequently reported acute harms of Ecstasy [53, 242].

A study of rats receiving subcutaneous injections of 9 mg/kg MDMA, just under half the LD50 of 20 mg/kg in rats housed together, reliably produced malignant hyperthermia in the context of warm ambient temperatures of 29°C and during social interaction [187]. At this dose, MDMA monotonically increased intracerebral heat production and muscle temperature while causing strong and sustained peripheral vasoconstriction, which inhibits heat dissipation. Social interaction on its own also induced metabolic brain activation and transient vasoconstriction in rats, which compounds the hyperthermic effects of MDMA observed at toxic doses and warm ambient temperatures. These effects are likely to be mediated through dopaminergic pathways [353, 354], which have been shown to be play a minor role in producing the effects of MDMA in humans [34].

4.4.7 Cardiovascular Toxicity

Injections of 20 mg/kg MDMA in conscious rats assessed by radiotelemetry (10.7 times the equivalent dose in humans), found that MDMA caused a prolonged increase in blood pressure [202]. In the same study, MDMA was found to produce mild isotonic contractions of aorta and vas deferens vascular tissue in anesthetized rats, but could also inhibit prejunctional contractions evoked by stimulation [202].

The elevation of blood pressure and increased heart rate produced by MDMA, similar to that produced by other sympathomimetic drugs, can lead to additional risks and complications [355-357], such as stroke, cardiac events, or other cerebrovascular events, including cerebral venous sinus thrombosis [358] and cerebral or subarachnoid hemorrhage [80, 359-363]. In two such cases, a previously existing underlying arteriovenous malformation appeared to play a role in the event [359, 361]. Intra-cardiac pressures, intra-arterial pressures, angiotensin II, pain, and adrenergic (α_2) central nervous stimuli can also influence AVP secretion [364]. Increased AVP concentration is described in several studies as a strong predictor of mortality in patients with chronic heart failure and acute heart failure, and contributes to increases in blood pressure [365]. As with any amphetamine, increased heart rate (tachycardia) and elevated blood pressure can also

lead to cardiac events, such as arrhythmias or myocardial infarction [366, 367]. Fatal dysrhythmias have been reported following heavy MDMA use, resulting in ventricular fibrillation and asystole. Individuals with underlying cardiac and/or pulmonary disease and preexisting conditions such as Wolff-Parkinson-White syndrome are especially at risk for heart failure and fatal arrhythmias. Although the presence of MDMA was rarely confirmed in reported cases, these types of events are all well-established complications of hypertension and can occur after use of amphetamines. There have been no such events to date in any clinical trial of MDMA.
Some researchers have expressed concern that MDMA activity at $5HT_{2B}$ receptors might be indicative of increasing risk of VHD with repeated use [24]. Studies in Ecstasy users indicated that only people reporting average lifetime exposure of 900 tablets had cardiac abnormalities indicative of potential VHD [247], and a case of VHD has occurred in a man reporting approximately 16 years of heavy Ecstasy use, from age 17 to 33 years old. [368]. No abnormalities were found in people reporting lifetime exposure of approximately 200 tablets in the same study. Echocardiographic readings in eight Ecstasy users also failed to find any cardiac abnormalities [45]. Since VHD-associated changes and VHD only occurred after extremely heavy Ecstasy use, they are unlikely to be a risk within the research or therapeutic context.

4.4.8 Hyponatremia

A number of case reports describe hyponatremia after uncontrolled, non-medical Ecstasy use [54, 369-371]. A recent meta-analysis showed that a moderate reduction of serum sodium concentration is associated with an increased risk of death in different pathologic conditions [372]. Relationships have been found between reduced plasma sodium, a measure of hyponatremia, and variations in COMT and CYP2D6 genotypes, possibly related to increased AVP and oxytocin release associated with MDMA [252]. Active doses of MDMA likely inhibit CYP2D6 in most individuals, as described in Section 5.2.1 Pharmacokinetics. Behavioral factors, including vigorous exercise and excessive consumption of water without an attempt to replace electrolytes, and an increase in the anti-diuretic hormones AVP and oxytocin, likely all contribute to this very rare but SAEs in Ecstasy users [32]. Women are generally more likely to exhibit hyponatremia than men [373, 374], including Ecstasy or MDMA related hyponatremia [54]. Heart failure is commonly associated with hyponatremia, and is also characterized by increased concentrations of AVP [375-377]. Hyponatremia has not occurred during a controlled clinical trial with MDMA.

4.4.9 Hepatotoxicity

In vitro studies and studies employing high, repeated doses of MDMA, estimated as being at least five times greater than expected in a clinical trial [378], report damage to liver cells [379-381]. Though many of these studies employed MDMA concentrations much higher than would occur after human ingestion, there are reports of liver disease in Ecstasy users. Studies in rats suggest a role of body temperature in promoting liver toxicity. A review of the literature highlights a number of potential factors, including body temperature and metabolism in preclinical studies and polydrug use, including alcohol, and environmental factors in humans [382]. Due to disparities in dosing and method, it is hard to establish whether these findings are relevant for liver toxicity in human Ecstasy users.

Hepatotoxicity (liver disease or damage) was reported in approximately 16% of 199 case reports from Ecstasy users in non-medical, uncontrolled settings, collected from the mid-1990s to 2001, making it the third most common serious adverse report in the literature. There appears to be more than one pattern of Ecstasy-related hepatotoxicity, and a number of factors, including polydrug use and setting of use may be involved [382]. Acute liver failure or hepatitis has

occurred after reported ingestion of a single Ecstasy tablet [383-386]. In other cases, hepatotoxicity has occurred after months of regular Ecstasy use [387]. Standard toxicity studies failed to find liver damage after MDMA in rats or dogs after 28 days of exposure [330], nor have any cases of liver disease arisen during controlled studies. Examinations of case reports and a number of *in vitro* studies suggest an association between hyperthermia and hepatotoxicity. However, liver disease also occurred in some individuals without the occurrence of hyperthermia, appearing after continued use and resolving after abstinence. These reports suggest a potential immunological mechanism. Since hepatotoxicity has been noted in Ecstasy users, *in vitro* and *in vivo* studies have examined the hepatotoxicity of MDMA. These studies show that high repeated doses of MDMA can impair liver cell viability *in vivo* [379], and can increase profibrogenic activity in cultured stellate cells [381] while reducing cell viability without producing lipid peroxidation *in vitro* [379, 388]. At higher ambient temperatures, a toxic dosing regimen was capable of increasing lipid peroxidation and activating apoptosis due to oxidative stress [389]. A single intraperitoneal dose of 20 mg/kg in rats was still capable of disrupting glutathione homeostasis, decreasing antioxidant enzyme activity, and lipoperoxidation activating apoptosis in one study [390]. However, peak liver exposure to MDMA in sponsor-supported studies should be approximately one-eleventh the concentration shown to impair cell viability in these studies. No cases of liver disease or hepatotoxicity have occurred in controlled clinical trials with MDMA. See Section 5.3.6 Hepatic Effects for discussion of liver panel results in sponsor-supported clinical trials.

4.4.10 Neurotoxicity

Repeated very high doses of MDMA in animals reduce total serotonin levels in the brain, impair transport of serotonin, and cause psychobehavioral changes such as increased anxiety [124, 226, 391-393]. In combination with other drugs or in high dose binge administration studies, MDMA may provoke serotonin syndrome. For example, rodents respond to high doses of MDMA by exhibiting flat body posture, forepaw treading and an erect tail ("Straub tail") [393]. These behaviors are considered indicators of serotonin syndrome. Doses used in most preclinical studies of neurotoxicity are at least five times the amount used in clinical trials or nonmedical settings, and can be as high as 20 times that amount. Studies in rodents and primates suggest that repeated high doses of MDMA could reduce regional serotonin, damage serotonin axons and cause neurotoxicity [124, 135, 394-397] and promote apoptosis in the hippocampus after 5 or 10 mg/kg MDMA given daily for 1 week [214]. However, the majority of these studies employed large doses of MDMA that overestimated human-equivalent doses, with findings now clearly indicating that doses used in nearly all rat and most primate studies are inappropriately high for comparison to use in clinical settings and are more pertinent toxicological effects of MDMA [78, 114, 119].

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

Many investigations have examined cognitive function in Ecstasy users with the goal of demonstrating long-term effects of purported neurotoxicity of Ecstasy. Rogers and colleagues

performed a meta-analysis on a large number of retrospective studies of Ecstasy users and various cognitive functions. Given methodological flaws in this type of analysis, the investigators cautiously concluded that there might be a significant effect of Ecstasy use on verbal memory, and a lesser effect on visual memory [53]. Retrospective designs and inappropriately matched samples continue to appear in the literature [398-400], even when using multiple control groups. Two meta-analyses of memory in Ecstasy users arrived at somewhat contradictory conclusions [401, 402]. Both detected an association between Ecstasy use and impaired performance on at least some measures of memory. However, one reported that this association had a medium to large effect size with no effect of Ecstasy dose [401], while the other reported that the association had a small to medium effect size with an Ecstasy dose effect, and that polydrug use itself contributed to impaired cognitive function [402]. A meta-analysis comparing current Ecstasy users and drug-using controls on visuospatial skills reported that current users performed less well on measures of visual recall, recognition and item production than controls [403], but found no significant relationship between lifetime Ecstasy use and visuospatial task performance. A longitudinal study comparing people who continued to use Ecstasy with those who did not do so detected lower performance on immediate and delayed visual memory [404]. In a second follow-up in the same sample reported lower scores in visual memory, at marginal significance and no further impairment [405]. An examination of the relationship between elements of Ecstasy use history and verbal memory reported that use in the past year, especially in men, was associated with impaired verbal memory [406]. The authors suggest that gender differences in polydrug use may be involved. A study comparing performance on a test of verbal memory in 65 ecstasy users enrolled in clinical trials of MDMA and an equal number of age and gender matched non-drug using controls from other trials failed to detect significant differences between the two groups [407]. This study employed a pre-determined measure of clinical significance, 1.5 times the average standard deviation of the healthy controls, and used a Bayesian statistical test suited for assessing a null hypothesis. It is notable that none of the subjects were enrolled in studies designed to compare cognitive function in ecstasy users, which may have reduced anxiety and potential risk of "stereotype threat" that may be faced by substance users completing assessments of cognitive function, which was done to reduce expectancy in the study [408].

The nature and strength of the association between regular Ecstasy use and any impairments in executive function remains inconclusive, with studies reporting conflicting results [5, 258, 259, 409, 410]. Findings from a study published in 2014 did not find differences in multitasking [301]. A meta-analysis comparing executive function in Ecstasy users and non-Ecstasy using controls found a significant effect of Ecstasy use on one component of executive function (updating), no effect on another (shifting) and mixed results when looking at other components (response inhibition and access to long-term memory) [411]. Polydrug use likely contributes to findings of impaired executive function seen in Ecstasy users [292, 412]. Current research has not settled the question.

Psychiatric problems after uncontrolled, non-medical Ecstasy use were reported in 22.1% of 199 case reports from the early 1990s to 2001, and are the most common reason for appearance at an emergency department [52, 55]. Psychiatric symptoms included affective responses, such as dysphoria, anxiety, panic, and psychotic response, as well as cases with mixed psychotic and affective features. The most common problem reported included panic, restlessness and psychotic response, as seen a systematic review and several epidemiological case series [53, 413]. The mechanisms behind Ecstasy-associated psychiatric problems remain unclear, but are likely the result of an interaction between pharmacology and individual susceptibility. The difficulty of assessing the frequency of these events is increased given that pre-existing psychiatric problems occur in people who choose to use Ecstasy [414] and findings of an association between use of Ecstasy and other drugs and self-reported symptoms of anxiety and depression. As described earlier, most cases of psychological distress after Ecstasy use resolved after supportive care [52, 55].

Anxiety responses associated with MDMA administration reported in controlled trials have resolved over time, usually either during the period of acute drug effect or with the waning of drug effects.

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

Intravenous MDMA doses that cause lethality in 50% of the cases, known as the LD50, are 97 mg/kg in mice, 49 mg/kg in rats, 14 to 18 mg/kg in dogs, and 22 mg/kg in monkeys [106]. LD50 may vary across strains, sexes, and housing conditions [415-417]. For example, LD50 in mice housed together is 20 mg/kg, which is considerably lower than in isolated animals [189, 418]. Reducing ambient temperature and administering the $5HT_{2A}$ antagonist ketanserin reduced lethality, suggesting that amplified elevation in body temperature and activity at serotonin receptors may promote lethality in group-housed mice given MDMA [189]. Considerable variation across studies in environmental factors, that are often underspecified in published reports, contribute to challenges in extrapolating findings in animal studies that may be relevant in epidemiological settings.

A number of SAEs, including fatalities, have been reported in humans after Ecstasy use in unsupervised and uncontrolled settings. These events are relatively rare given the prevalence of Ecstasy use [49, 50]. These include hyperthermia (potentially arising from "serotonin syndrome"), psychiatric problems, hepatotoxicity (secondary to hyperthermia), cardiac disorders and hyponatremia [49, 52-54, 419]. Set and setting likely play a role in the development of some Ecstasy-related AEs, such as vigorous exercise, lack of attention to somatic cues, and too little or too much hydration combined with pharmacological action on AVP resulting in hyperthermia or hyponatremia [51, 371]. Even if ambient temperature does less to moderate the effects of MDMA on body temperature than originally believed based on animal studies, other environmental and behavioral factors, as those related to vigorous exercise, may be involved. It is important to note that not all reports of AEs in Ecstasy users provide information on whether MDMA was detected in plasma or other fluids, with some relying on self-report or the reports of friends as to identity of substances consumed. Reports indicating detectable MDMA will thus be the best indicators of an actual association. Unexpected drug-related SAEs have not occurred in any of the human MDMA research studies thus far.

While case reports do not provide an appropriate basis for estimating the relative frequency of these events, they can provide information on the possibility of an event occurring. Most Ecstasy-related emergency department admissions are the result of people experiencing anxiety or panic reactions after use and involve supportive care only [52, 55, 420]. An extensive systematic review reached similar conclusions concerning the frequency and nature of emergency department admissions, though also noting that owing to complexities of nonmedical and recreational use, the researchers found it hard to establish a lethal dose [53]. However, a pair of case series drawn from two different events suggests a general relationship between estimated dose and number of emergency department admissions after exhibiting seizures, unresponsiveness or hyperthermia, with both series reporting high doses of MDMA (230 and 270 mg) in sample tablets or capsules [421, 422]. As is the case with fatalities associated with reports of Ecstasy use, medical emergencies after Ecstasy use are more likely to occur in men [52]. Individuals consuming Ecstasy with pre-existing conditions are at increased risk when consuming drugs of unknown purity, identity, and dose in uncontrolled settings.

Table 2: Summary of Published Morbidity and Mortality Reports

Body System	Reports	Morbidity Reports	Mortality Reports	Total Reports
Thermoregulatory Disorders	Hyperthermia, Hyperprexia, Rhabdomyolysis, Hypoglycemia	135 [80, 421, 423-438]	43 [80, 217, 421, 423, 435, 439, 440]	178
Cardiac Disorders	Cardiac valve disease, Ventricular fibrillation, Cardiac arrest, Arrythmia, Myocardial infarction, Generalized tonic-clonic seizure, Acute coronary syndrome, Myocardial necrosis, Cardio-respiratory arrest, Cardiomyopathy	15 [367, 368, 441-447]	12 [366, 423, 448-452]	27
Osmoregulatory Disorders	Cerebral oedema, SIADH, Urinary retention, Hyponatremia, Acute renal failure	18 [453-465]	6 [367, 466-470]	24
Hepatobiliary Disorders	Acute fulminant hepatitis, Liver disease, Disseminated intravascular coagulation	4 [386, 447, 471, 472]	5 [473-477]	9
Blood and Lymphatic System Disorders	Aplastic anemia	3 [478, 479]	1 [480]	4
Injuries, Poisonings, and Procedural Complications	Anaphylactic shock, Facial rash eruption	1 [481]	1 [482]	2
Nervous System Disorders	Hemorrhage, Infarct, Hippocampal sclerosis (suspected), Encephalopathy, Amnestic syndrome	13 [355, 356, 483-490]	0	13
Dental Disorders	Xerostoma, Bruxism, Dental erosion	15 [491-493]	0	15

Body System	Reports	Morbidity Reports	Mortality Reports	Total Reports
Psychiatric Disorders	Psychotic episode, Depressive episode, Obsessive-compulsive disorder, Autoenucleation	4 [494-496]	0	4
Respiratory, Thoracic, and Mediastinal Disorders	Subcutaneous Pneumomediastinum Epidural pneumatosis, Diffuse alveolar hemorrhage, Asthma	9 [366, 497-504]	0	9
Opthalmic Disorders	Lagophthalmos, Keratopathy, Bilateral sixth nerve palsy	4 [505, 506]	0	4
Injuries, Poisonings, and Procedural Complications	Unknown cause of death	0	204 [366, 507]	204

Four hundred ninety-three case reports, with 272 of these resulting in death, associated with Ecstasy use from 1986 through 2016 are summarized in Table 2. Of these 272, 32 were described in a cumulative 2002 literature review with incomplete citations of sources, and are reported in addition to individual case reports of morbidities in the literature [423]. Detectable levels of MDMA in blood or urine are reported in less than half of these case reports, and range from 50 ng/mL (reported as less than 0.05 mg/L) in the case of anaphylactic shock [482] to 1500 ng/mL (reported as 1.5 mg/L) in a fatal case of hyperthermia and rhabdomyolisis [440]. It is more difficult to associate events with MDMA when the compound is not detected or when detection is for amphetamines in general. Some events, such as VHD, acute hepatitis with gallbladder inflammation, liver disease, or urinary retention occurred in individuals who self-reported daily use for months to years prior to the event. In the majority of the 202 poisoning cases with unknown cause of death, Ecstasy was used in combination with opiates by drug addicts who died in the UK and Wales between 1996 and 2002 [507], and polysubstance use is common in the majority of serious reports presented.

Thermoregulatory disorders play a part in the development of a constellation of disorders across body systems described below. Primary symptoms are hyperthermia resulting rhabdomyolysis described in 135 reports of morbidity and 43 reports of mortality, constituting the most common acute adverse effect associated with Ecstasy. Sympathomimetic effects of MDMA, at unknown doses and purity, in combination with permissive factors in uncontrolled settings, can lead to serious reports of acute and persisting adverse effects on multiple organs. In research settings, the risk of hyperthermia is limited by controlling ambient temperature, conducting treatment sessions in relaxed, private environments, and generally limiting permissive factors.

Cardiac disorders associated with Ecstasy in the context of hyperthermia resulted in 15 reports of morbidity and 12 reports of mortality. Several fatal cases of cardiac arrest were reported. In addition, a non-fatal cardiac arrest occurred in the context of a genetic arrhythmia disorder, catecholaminergic polymorphic ventricular tachycardia [442]. Apparent use of Ecstasy, with concurrent use of other amphetamines during pregnancy, was associated with seizures and myocardial infarction [445, 446]. As evidenced by these reports, individuals consuming Ecstasy

with pre-existing conditions that can influence cardiovascular and cardiac function are at increased risk when consuming drugs of unknown purity, identity, and dose in uncontrolled settings.

Osmoregulatory disorders associated with Ecstasy in the context of hyperthermia resulted in 18 reports of morbidity and six reports of mortality, with acute renal failure (ARF) as the most common cause of death. As described in Section 4.4.8 Hyponatremia, increased AVP secretion caused by MDMA in combination with permissive factors in uncontrolled settings can lead to serious reports of acute and persisting adverse effects on multiple organs, including the liver. Individuals consuming Ecstasy with pre-existing conditions that can influence renal function are at increased risk. In response to this risk, many users tend to overcompensate with excessive consumption of water, leading to dilutional hyponatremia. Prevention of hyponatremia with limited consumption of electrolyte containing fluids and controlled ambient temperatures are required to preserve the body's homeostatic maintenance of fluid balance.

Hepatobiliary disorders associated with Ecstasy use resulted in four reports of morbidity and four reports of mortality. One of the mortality reports happened 1 week after Ecstasy use and was consistent with acute fulminant hepatitis in the absence of viral infection. This patient died despite liver transplantation efforts [473]. Typically, mortality results from disseminated intravascular coagulation (DIC) caused by platelet dysfunction associated with liver failure. Non-fatal morbidity reports range from acute hepatitis associated with daily usage of five to eight tablets of Ecstasy for 3 months in combination with alcohol [471] to liver damage in combination with congestive cardiomyopathy [447]. Given that polysubstance use and prior insult to liver function cannot be ruled out, the frequency of isolated serious hepatotoxicity cases in the absence of hyperthermia are rare among serious reports associated with Ecstasy use. Hepatotoxicity is more common among serious reports in combination with hyperthermia and acute renal failure.

Blood and lymphatic system disorders associated with Ecstasy use resulted in three morbidity reports and one mortality report of aplastic anemia. The death after aplastic anemia occurred from complications of immunosuppressant therapy followed by an allogenic stem cell transplant, 17 months after the first admission [480]. The patient had initially presented with progressive weakness and epistaxis, resulting from daily Ecstasy use for 7 months, combined with heavy alcohol intake. Further examination revealed the replacement of bone marrow tissue with fatty deposits, likely due to alcohol consumption and exacerbated by chronic Ecstasy use. Three reports of morbidity ranged in prior Ecstasy use levels from once to four times in the prior year, with two cases spontaneously resolving within 2 months and the treated case failing immunosuppressive therapy and recovering 4 months after subsequent bone marrow transplant [480].

The report of possible anaphylactic shock and subsequent death occurred in a 13-year old girl who had at least one previous exposure to Ecstasy [482]. Her friends reported that she experienced swelling lips after her first exposure. After approximately 1.5 tablets, the girl experienced nausea and vomited, and later had difficulty breathing. On admission she was hypothermic and hypotensive. A low level of MDMA (<0.5 mg/dL) was detected in blood. None of the other individuals consuming tablets from the same batch underwent similar experiences. Autopsy found a massive brain edema as well as laryngeal oedema and lung congestion. Chemical analyses ruled out hyponatremia. The reaction may have been to MDMA or to an adulterant in the tablet. The authors of the report do not report whether tablets were assessed for contents.

Memory difficulties arising immediately after Ecstasy use have been reported in a sporadic user [487]. The memory difficulties arose in a man reporting use of Ecstasy five or six times, with

confusion and cognitive impairment reportedly occurring after taking a single tablet at a party. Cognitive function was assessed 7 years later. Imaging showed signs of hippocampal sclerosis. It is not clear from the report whether the individual used Ecstasy prior to or after this event. The individual had hypertension, raising questions concerning possibility of a cerebrovascular event. In a neurological serious report with 0.83 ng/mL MDMA detected in the hair of a girl who developed encephalopathy [486] during chronic low or moderate Ecstasy use, cognitive function and memory problems associated with neurological damage was reported. Upon cessation of use 16 months later, extensive hippocampal remodeling was reported assessed through PET scans. This finding is consistent with hippocampal dendritic spine remodeling observed in rats receiving 20 mg/kg MDMA for four days intended to simulate chronic usage in humans [508], however the clinical presentation was also similar to CNS herpes infection, so it is difficult to attribute this isolated case report to only Ecstasy use. Two reports have identified bilateral lesions in the globus pallidus of ecstasy users during magnetic resonance imaging (MRI) or autopsy, with a third report finding hippocampal changes in imaging associated with amnestic syndrome [488-490]. Due to the retrospective and infrequent nature of these reports, it is difficult to determine causality.

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

4.6 Abuse Potential in Nonclinical Studies

Studies in Ecstasy users and animals suggest MDMA possesses some abuse potential, but not nearly that of amphetamine. Mice, rats, and monkeys self-administer MDMA, indicating that MDMA has rewarding properties in animals [509-511]; however, the rate and response-acquisition of self-administration is much lower than other drugs of abuse, such as cocaine or heroin. In rodents, acquisition of MDMA self-administration requires a lengthy training period with consecutive sessions [510, 512, 513]. Physical dependence and drug withdrawal was investigated by treating mice with 10 mg/kg i.p. MDMA twice daily for 5 days. Results showed that mice did not exhibit aversive/dysphoric or anxiogenic behaviors after treatment, indicating that high doses of MDMA do not induce classical symptoms of physical dependence [514]. Monkeys choose to self-administer MDMA in doses equivalent to or only slightly higher than doses used by humans [509], 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 [512, 513]. Taken together, results in animals suggest that the abuse liability of MDMA is moderate.

Drug discrimination studies investigating the discriminative stimulus effects of MDMA as either hallucinogenic or stimulant have reported inconsistent findings. Some drug discrimination studies have shown MDMA to completely substitute for S-(+)-amphetamine in rats [634], monkeys [635], and pigeons [636]; where as other reports did not [637]. In a two-lever procedure, MDMA did not substitute for the hallucinogens (+)-lysergic acid diethylamide (LSD) or (+)-2,5-dimethoxy-4-methylamphetamine (DOM) [66, 638-639]. A three-lever procedure found that LSD produced dose-dependent increased substitution for MDMA while neither cocaine nor 2,5-dimethoxy-4-bromoamphetamine (DOB) substituted for it [640]. Serotonin and dopamine may be involved in producing stimulus characteristics in rats [641]. On the other hand, MDMA has been shown to substitute for mescaline [638]. Given MDMA's unique pharmacological profile and it's ability to produce stimulant-like, mild hallucinogen-like, and empathogenic effects, in 1986 Nichols coined a novel pharmacological class, the 'entactogens' [66].

Research of Ecstasy dependence comes from a combination of published case studies and assessment of symptoms based on the Composite International Diagnostic Interview,

the Diagnostic and Statistical Manual of Mental Disorders Version IV (DSM-IV), and/or the Severity of Dependence Scale [521]. Of the small number of individuals assessed in a representative sample of Munich residents aged 14 to 24, only 1% were diagnosed with Ecstasy abuse and 0.6% with dependence [520], though other reports of large (N=173) but non-representative samples, including subjects recruited from substance abuse programs, reported 30% (N=52) had used Ecstasy and of these, 43% met DSM-IV criteria for dependence [519]. In a large Australian sample (N=329), approximately 25% of polydrug users wanted to reduce their Ecstasy use and 20% had received treatment for an Ecstasy-related problem, although this sample likely had an over-representation of chaotic intravenuous polydrug users [522]. In a study of self-reported cravings in Ecstasy users, exposure to Ecstasy-related cues induced greater subject ratings of craving. Although over 50% of subjects agreed on some level with two or more statements regarding Ecstasy-related craving, the average score for craving was negative [523]. It also appears that MDMA has fewer or less intensely rewarding effects than stimulants, and even heavy Ecstasy users fail to report the intensive patterns of use seen with other stimulants [2, 4, 515]. Based on two structural analyses, Ecstasy dependence is bifactorial [517]. Although Ecstasy dependence does have a compulsive use factor as well as an escalating use factor, withdrawal symptoms do not include significant physical symptoms such as alcohol, cocaine, methamphetamine, opioids, and tobacco [516, 518]. In a prospective longitudinal study (N=2446), German polydrug users reported low prevalence of initial Ecstasy abuse or dependence, as well as substantial decline in use factors at 12-month follow-up, suggesting that Ecstasy use is a self-limiting transient phenomenon in many cases [520]. Features of Ecstasy abuse and dependence in humans are consistent with preclinical findings in self-administration studies of moderate abuse liability that is greater than that for serotonergic hallucinogens, but less than that for stimulants [510, 524].

5.0 Effects in Humans in Clinical Settings

5.1 History of Use in Clinical Settings

Shulgin and Nichols were the first to report on the effects of MDMA in humans [59]. In the 1970s, psychotherapists used MDMA-assisted psychotherapy to treat psychological disorders, including anxiety [65]. Legal therapeutic use continued until its placement on the U.S. list of Schedule I drugs in 1985 [64, 68, 525]. An estimated 500,000 doses of MDMA were administered during psychotherapy sessions in North America prior to its scheduling [57, 525]. A few uncontrolled human studies of MDMA occurred in the 1980s [44, 62], including Greer and Tolbert's study of MDMA in a psychotherapeutic context.

Controlled human studies of MDMA commenced in the mid-1990s with a MAPS funded investigator-initiated Phase 1 dose-response safety study [47, 526]. MAPS also funded a Phase 2 investigator-initiated dose-response safety and efficacy pilot study in Spain that was terminated early due to political concerns. This study enrolled six subjects, with four receiving a single session of MDMA-assisted psychotherapy without any safety concerns and experiencing some PTSD symptom reduction [527].

Based on past reports of MDMA use, preclinical studies and the results from these investigator-initiated trials with MDMA, the sponsor launched a Phase 2 Clinical Development Program in 2001 to develop MDMA-assisted psychotherapy for the treatment of chronic PTSD under U.S. IND. Eight sponsor-supported Phase 2 studies of MDMA-assisted psychotherapy for PTSD have been conducted. Two have been published, one main study with an extension in three subjects who relapsed in the U.S. (MP-1, MP1-E2) [41, 42], and one in Switzerland (MP-2)[43]. Four additional studies have completed treatments (MP-4, MP-8, MP-12) and are in follow-up, one

study in Israel was terminated early (MP-3) and re-initiated with a new study team (MP-9) and has completed enrollment.

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

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

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

There are three Phase 2 studies currently in follow-up (MP-8, MP-12, MP-4) and one that is completing treatments (MP-9). These studies explore the reproducibility of treatment outcomes of MDMA-assisted psychotherapy in people with chronic PTSD that failed to respond to at least one course of psychotherapy or at least one course of pharmacotherapy. Two of the randomized, blinded studies are taking place in the U.S. MP-8 (N=26) compares 30 mg versus 75 mg versus 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose, in military veterans, firefighters and police officers ("first responders") with service-related PTSD, with an average age of 37.2±10.3 years. MP-12 (N=28) compares 40 mg versus 100 mg

versus 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose, in subjects with PTSD from any cause, with an average age of 42.0±12.9 years. The Canadian study MP-4 (N=6) compares placebo to 125 mg initial dose of MDMA, with an optional supplemental dose equivalent to half the initial dose, in subjects with an average age of 47.7±6.0 years, and MP-9 (N=10) in Israel compares an initial dose of 25 mg to 125 mg MDMA, with an optional supplemental dose equivalent to half the initial dose, in subjects with an average age of 36.7±8.0 years.

The sponsor is also supporting two additional Phase 2 studies of MDMA-assisted therapies in parallel indications: one for treatment of social anxiety in autistic adults (MAA-1, N=12), and another for anxiety associated with a life-threatening illness (MDA-1, N=18). Subjective effects, mood, and reactions are also being assessed in the ongoing Phase 1 placebo-controlled study of MDMA-assisted psychotherapy, in healthy volunteers who have completed training in manualized MDMA-assisted psychotherapy (MT-1).

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

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

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

5.2 Pharmacology in Humans

As of 2015, the sponsor has not conducted studies on the pharmacodynamics or pharmacokinetics of MDMA, but relies on published literature. Beginning in the early to mid-1990s, several research teams conducted studies of the pharmacodynamics and pharmacokinetics of MDMA [10, 14, 22, 29, 116, 327, 528-530] without receiving sponsor support. Findings from these teams are described below, with specifics of metabolism detailed in Section 5.2.1 Pharmacokinetics.

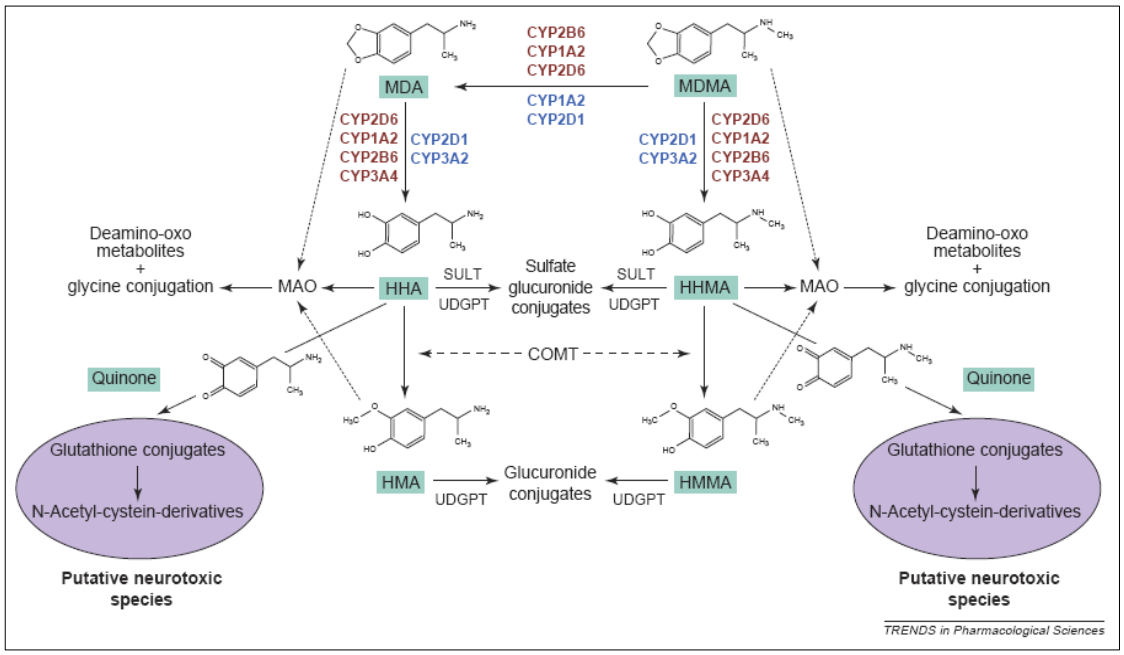
5.2.1 Pharmacokinetics

Onset of MDMA effects occurs 30 to 60 minutes after administration [8, 9], peak effects appear 75 to 120 minutes post-drug [7, 10-12], and duration of effects lasts from 3 to 6 hours [10, 12, 13], with most effects returning to baseline or near-baseline levels 6 hours after final drug administration. Self-reported duration of effects may increase as the dose of MDMA increases [7]. Administering a second dose of MDMA 2 hours after the initial dose, twice that of the initial dose, does not significantly extend the duration of measureable physiological or subjective effects [328]. Orally administered MDMA has a half-life of 7 to 8 hours in humans, with one report listing a half-life of 11 hours [531], and half-life is marginally extended if an additional dose is administered 2 hours after an initial dose [328]. Metabolites of MDMA are summarized in Figure

1 [532-537]. Metabolites are primarily excreted as glucuronide and sulfate conjugates [534]. Studies examining metabolism of 100 mg MDMA reported excretion values similar to those reported by de la Torre and associates [118, 531, 538-540]. MDMA and its metabolite MDA appear in oral fluid samples at much higher concentrations than plasma, for 24 to 48 hours for the former and 12 to 47 hours for the latter after oral administration of 1 to 1.6 mg/kg MDMA [541]. Urinary excretion of the MDMA metabolite HHMA after 100 mg MDMA in four men was 91.8±23.8 mol and 17.7% recovery [540]. By contrast, urinary recovery of the major metabolite HMMA after 100 mg was 40% [542]. As was the case for maximal plasma values, urinary recoveries for MDMA and MDA were higher when a second dose of 100 mg MDMA was administered 24 hours after an initial dose of 100 mg MDMA when compared with a single dose [118]. 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 [543], suggesting that secondary metabolism of MDMA continues during this period. Findings support the enantioselective nonlinear metabolism of MDMA and its metabolites measured in blood and urine [544, 545].

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 [328], findings further supported by examining plasma MDMA after two doses of 100 mg given 4 hours apart [546], likely due to metabolic autoinhibition. Comparison of pharmacokinetic-pharmacodynamic relationships for MDMA reveals acute pharmacodynamic tolerance. Despite 8 hours of plasma half-life of MDMA, and persistent high drug levels in the blood, most pharmacodynamic effects of the initial dose rapidly return to baseline within 4 to 6 hours [530]. These findings suggest that intensity of most subjective and physiological effects of MDMA would not be significantly impacted by the supplemental doses in sponsor-supported studies due to acute tolerance to its prototypical effects [546]. This acute tolerance could be caused by functional depletion of stores of serotonin so that no more can be released despite MDMA still being present [530], or suggests that MDMA transport into intracellular spaces is saturable due to limited transport capacity [127]. Additionally, reversible inhibition of tryptophan hydroxylase as observed in rodents [20], or internalization of serotonin reuptake transporters from the plasma membrane leading to less serotonin release [78], would support self-limiting effects of MDMA. On the other hand, although SERT can be internalized, evidence suggests that accumulation of extracellular serotonin stimulated by MDMA affects SERT trafficking by perpetuating cell-surface SERT expression, but in contrast promotes internalization of DAT and NET [127, 547].

Figure 1: Metabolism of MDMA in Humans



Metabolism of MDMA in humans (in red) compared to metabolism in rats (in blue). Reproduced with permission of R. de la Torre [113].

MDMA is metabolized in the liver by several cytochrome P450 CYP enzymes, including CYP1A2, CYP3A4, and CYP2D6. It is likely that active doses of MDMA inhibit CYP2D6 function, as measured by examining the effects of MDMA on dextromethorphan metabolism. Inhibition of CYP2D6 by MDMA was demonstrated first in a physiological model derived from data collected after oral administration in humans [548]. O'Mathuna and colleagues present evidence that CYP2D6 activity may not fully recover until 10 days after MDMA [549, 550]. 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 [327]. In contrast, MDMA may produce increased activity of the enzyme CYP1A2, as evidenced by comparing caffeine metabolism before and after MDMA [551]. The enzyme COMT and monoamine oxidase may also be involved in the metabolism of MDMA [542]. At least one variation in COMT genotype may affect MDMA elimination rate (K_e) and systolic blood pressure (SBP) after MDMA [552]. As a monoamine reuptake inhibitor that leads to monoamine release and inhibits monoamine oxidase-A [132] combining MDMA with a monoamine oxidase inhibitor (MAOI) medication presents a risk for provoking serotonin syndrome and increases in sympathetic activity. Fatalities have occurred apparently as a result of combining MAOI medications with MDMA [133, 134]. For this reason, MAOI medications are tapered for at least five half lives of the medication and active metabolites, plus 1 week for symptom stabilization in sponsor-supported studies.

Researchers have attempted to compare MDMA pharmacokinetics in humans and other species, including other primates, as discussed in Section 4.2.1 Pharmacokinetics in Animals and Section 5.2.1 Pharmacokinetics. These investigations sought to establish human-equivalent doses given nonlinear pharmacokinetics. Doses that researchers assumed to be human-equivalent produced greater plasma concentrations. However, duration of exposure expressed in half-life was often shorter. For example, a dose of 1.6 mg/kg MDMA produced a half-life of 8.4 hours in a small sample of humans while a dose of 2.8 mg/kg had a half-life of 2.1 hours [119]. A dose of 7.4

mg/kg in squirrel monkeys, four times a human-equivalent dose and never administered in a human trial, had a half-life of 3.4 hours [107]. Researchers have detected nonlinear pharmacokinetics of MDMA in all species studied to date, leading Mueller and colleagues to conclude that a preclinical study cannot accurately and simultaneously model human-equivalent plasma levels and equivalent duration of exposure [119].

5.2.2 Pharmacodynamics

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

Many researchers categorize MDMA as belonging to a unique class of drugs referred to as the Entactogens [13, 66], defined as substances that produce changes in mood and social interaction, as well as feelings of interpersonal closeness and changes in perception. MDMA shares some of the pharmacological effects of stimulants and serotonergic hallucinogens [8, 10, 11, 553], as well as a small number of pharmacologically related compounds, such as MDE [553]. Initially, narrative reports and surveys supported the social cognitive effects of MDMA or Ecstasy [2, 234, 235, 554]. Controlled trials detected self-reported empathy or closeness to others in healthy volunteers [7, 12, 91], and starting in the late 2000s to 2010s, controlled studies measured effects of MDMA on social cognition or emotion [29, 30, 35]. Although researchers have offered several models and explanations for the effects of Entactogens, it appears that serotonin and norepinephrine release play a significant role in producing at least some of these effects. Indirect action on $5HT_{1A}$ or $5HT_{2A}$ receptors and neuroendocrine responses such as increases in the hormones oxytocin, AVP, prolactin, and cortisol may also play a role in producing the unique effects of MDMA.

In addition to neuroendocrine and norepinephrine-mediated effects, MDMA may target similar binding sites on the SERT, as do already approved PTSD medications Paxil and Zoloft, which are both SSRIs. Similar to the SSRI Prozac, MDMA also inhibits MAO-A to extend presence of serotonin in the synaptic cleft [132]. Pre-treatment or co-administration studies of SSRIs with MDMA appear to attenuate or eliminate most subjective, physiological and immunological effects of MDMA due to competition for binding sites on the SERT which may prevent transporter-mediated serotonin release [91, 555-558]. Pre-treatment or co-administration with SSRIs attenuates serotonergic effects of MDMA on mood and perception, without influencing specific effects, such as nervousness or excitability [555]. Some researchers report that SSRIs attenuate MDMA-induced increases in heart rate and blood pressure [91, 556], while others report that SSRIs only attenuate elevated heart rate [558]. Additional effects of each SSRI beyond reuptake inhibition on production, release, and degradation of serotonin are likely responsible for variations between SSRI co-administration findings. All three studies of SSRI pre-treatment suggest that co-administration of SSRIs with MDMA is safe, but the combination prevents or significantly reduces the subjective effects of MDMA. The role of serotonin release on the potentially therapeutic effects of MDMA-assisted psychotherapy has yet to be investigated, however reduced feelings of sociability and closeness to others after paroxetine pre-

administration suggests that serotonin release is at least partially involved in prosocial effects that are thought to be therapeutically relevant [91]. These subjective effects are predominately mediated by direct or indirect action on $5HT_{2A}$ receptors [92, 233, 559], with at least one study concluding that the effects of MDMA upon positive mood are at least due in part to $5HT_{2A}$ receptor activation [92]. In contrast, the $5HT_{1A}$ receptor appears to be partially involved in producing the subjective effects of MDMA [92, 231-233]. Co-administration of the beta-blocker and $5HT_{1A}$ antagonist, pindolol, along with 1.6 mg/kg MDMA to 15 men attenuated self-reported "dreaminess" and pleasantly experienced derealization after MDMA without attenuating MDMA-related reduction in performance on a task requiring visual attention, and co-administration of pindolol failed to alter the acute effects of 75 mg MDMA on self-reported mood [92, 231].

Human MDMA studies suggest that norepinephrine release also contributes to the pharmacodynamic, physiological and psychological effects of MDMA [205, 208, 560, 561]. Tricyclic antidepressants, as well as many of the current antidepressant medications, are known to promote norepinephrine signaling, as does MDMA. Studies with the norepinephrine uptake inhibitor reboxetine, and the α_1-adrenergic receptor antagonist doxazosin, suggest that norepinephrine plays a role in the effects of MDMA on blood pressure and subjective effects of positive mood and excitement [206, 560], but not in "entactogenic" or "empathogenic" effects. Most of the psychostimulant-like and psychological effects of MDMA are blocked after administration of the dual selective Serotonin and norepinephrine uptake inhibitor (SNRI) duloxetine [208, 561]. There is evidence that norepinephrine and serotonin may play a role in the elevation in the neuroendocrine hormone copeptin, the C-terminal precursor of pre-pro-AVP, detected in women acutely after MDMA administration [561]. Some *in vitro* findings with human monoamine transporters expressed in cells indicate that MDMA displays a higher affinity for the NET than the serotonin or dopamine transporter, while still producing greater detectable release of serotonin versus norepinephrine, suggesting a role for both transmitter systems [127]. As the NET unexpectedly has a greater affinity than the DAT for dopamine, it preferentially clears dopamine in brain areas where there is a greater concentration of NET, such as the frontal cortex [562]. The relative affinities of MDMA for various monoamine reuptake transporters, and the affinity of the respective transporters for each neurotransmitter, can thus influence the selectivity of signaling pathways MDMA activates in a region-specific manner depending on transporter density and availability.

Some MDMA effects on human mood and anxiety may be attributed to dopamine release based on the finding that pretreatment with haloperidol, a dopamine receptor antagonist with partial selectivity for the D_2 receptor subtype, diminished MDMA-induced positive mood and increased anxiety [563]. However, the control group receiving haloperidol alone also experienced dysphoric mood, suggesting that this finding may overestimate the dopaminergic effects of MDMA. Studies comparing MDMA with the dopaminergic and adrenergic drug methylphenidate (Ritalin) suggest that dopamine release and inhibition of uptake play a minor role, if any, in producing the effects of MDMA [34]. Co-administration of MDMA with the potent dopamine reuptake inhibitor methylphenidate neither enhanced nor attenuated the effects of MDMA [530]. MDMA, but not methylphenidate, increased trust, openness, and closeness to others. Co-administration of MDMA with the dopamine reuptake inhibitor bupropion prolonged, but did not reduce subjective effects of MDMA, supporting that dopamine does not have a part in MDMA effects on mood [564].

MDMA produces a robust increase in the neurohormone oxytocin [29], a finding first seen in a naturalistic study that reported elevated levels of oxytocin in clubgoers with detectable blood MDMA levels when compared to clubgoers without detectable levels of MDMA [32], as described in Section 4.3.5 Neurobiological Effects. It is likely that all neuroendocrine changes are part of a signaling cascade downstream of monoamine release. Exogenous oxytocin increases trust and improves accuracy of emotion perception, and increased cortisol, in some

circumstances, may serve as a signal to seek affiliation or to increase positive mood [565-568]. However, studies comparing increases in empathy or prosocial effects of MDMA with intranasal oxytocin have failed to find indications that the two substances produce similar effects, with MDMA producing greater feelings of sociability and emotional empathy than oxytocin [63, 569]. Peripheral oxytocin has been suggested to be a reliable indicator of central oxytocin, but peripheral effects of oxytocin need to be ruled out when assessing central effects [570]. The potential significance of elevated oxytocin in producing changes in social cognition are discussed in Section 5.3.8.3 Social Effects, and include potentially therapeutic effects, such as increased feelings of closeness to others or greater ability to detect expressions of positive mood in others.

MDMA acutely increases cortisol, prolactin, and adrenocorticotropic hormone concentrations in a dose dependent manner [9, 12, 19, 30, 47, 118, 526, 572-574], whereas growth hormone levels are unchanged by up to 125 mg MDMA [9]. Increases in cortisol and prolactin peak at about 2 hours after MDMA administration [9, 47]. A second dose of 100 mg MDMA, given 4 hours after an initial 100 mg, produces a second increase in cortisol during an interval when cortisol levels are declining [575], and a dose of 100 mg MDMA, given 24 hours after an initial dose, stimulates a greater release of cortisol but not prolactin [118]. In a study of the effects of 0.5 and 1.5 mg/kg MDMA in eight people, there was a trend for increased levels of the hormone dehydroepiandrosterone (DHEA) after 0.5 mg/kg MDMA, and a significant increase after 1.5 mg/kg MDMA, with peak levels appearing 2 to 3 hours post-drug [12]. A crossover study comparing the effects of MDMA and methylphenidate found that MDMA increased serum cortisol while methylphenidate did not, and that neither drug altered testosterone levels [574]. These findings suggest a relationship between serotonin release and increased serum cortisol. Pre-treatment with the cortisol synthesis inhibitor metyrapone blocked MDMA-induced increase in cortisol levels in blood without preventing impaired performance on verbal memory tasks or altering the effects of MDMA on mood [572]. A study investigating the emotional effects of MDMA found no correlation between those changes and the MDMA-induced increases in oxytocin, cortisol, and prolactin [573].

The pharmacological basis for reported acute shifts in memory, including impaired visual recall and improved recall for life events, after MDMA administration remains undetermined. Initial findings suggest a relationship between MDMA and activation of temporal areas in the brain and response to positive memories, as well as increases in medial PFC and response to negative memories [36]. It is possible that elevation in cortisol could be tied to specific acute effects on mood or memory. Another study found MDMA-associated changes in inferior parietal lobule and acute impairment in working memory [576]. Animal studies have postulated a role of Ach release triggered by upstream serotonin and dopamine neurons in MDMA-induced shifts in memory described above. A human study revealed no difference in MDMA-induced memory changes following pretreatment with the cortisol synthesis inhibitor metyrapone or the α_7/nAchR7 receptor antagonist memantine, suggesting cortisol is not involved in these effects [572, 577]. It is unclear what contributions, if any, elevated neuroendocrine levels make to the subjective and memory effects of MDMA.

5.3 Safety of MDMA in Humans

Safety data from studies in controlled research settings show that MDMA produces sympathomimetic effects that include statistically significant, self-limiting increases in body temperature, heart rate, and blood pressure that are likely to be transient and well tolerated by healthy individuals [7, 9, 10, 12, 26, 41-47, 526, 527]. Risks posed by elevated blood pressure are addressed in clinical trials by excluding candidates with a history of cardiovascular or cerebrovascular disease or with pre-existing uncontrolled hypertension and by monitoring blood pressure and pulse during MDMA-assisted experimental sessions. Common reactions from

MDMA research studies are transient and diminish as drug effects wane during treatment sessions and over the next 24 hours. In studies conducted with and without sponsor support in controlled clinical settings, with 1180 individuals exposed to MDMA, there have been no published or reported unexpected drug-related SAEs to date, and expected SAEs have been rare and non-life threatening. One subject to date experienced an expected related SAE (increased premature ventricular extrasystoles in MP-8), and 10 unrelated SAEs after drug administration have been reported in MAPS-sponsored clinical trials.

All sponsor-supported data presented in this IB was collected through 01 October 2015. There are three completed (MP-1, MP-2, MP1-E2) and four ongoing Phase 2 studies of MDMA-assisted psychotherapy in people with PTSD that have completed enrollment (MP-8, MP-12, MP-4, MP-9). A Phase 2 study of MDMA-assisted therapy treating social anxiety in autistic adults (MAA-1) and another Phase 2 study of MDMA-assisted psychotherapy treating anxiety associated with life-threatening illness (MDA-1) are ongoing. Safety is addressed and closely monitored through several measures in these studies. Vital signs, concomitant medications, unexpected and expected AEs are collected in all studies. Suicidal ideation and behavior are formally measured with the Columbia Suicide Severity Rating Scale (C-SSRS) in all but MP-1 and MP-2. One completed (MP-1) and two ongoing studies (MP-12, MP-4) measure cognitive function before and after treatment. Psychological distress during psychotherapy sessions is assessed in all studies with the single-item Subjective Units of Distress (SUD) scale.

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

Physiological effects of MDMA-assisted psychotherapy in sponsored studies are similar to those reported in studies conducted outside of sponsor support, including elevated blood pressure, body temperature, and heart rate. The following common reactions are found in published literature and are collected in the sponsor's Phase 2 clinical trials: anxiety, depressed mood, insomnia, obsessive rumination, restlessness, irritability, headache, disturbance in attention, dizziness, parasthesia, judgment impaired, hypersomnia, nausea, diarrhea, fatigue, asthenia, feeling cold, muscle tightness, decreased appetite, hyperhidrosis, disturbed gait, dry mouth, thirst, sensation of heaviness, somnolence, and nystagmus. These common reactions are transient and diminish as the drug is metabolized during treatment sessions and excreted over the next 24 hours, with the majority of reactions resolving within several days and up to 1 week after dosing. Among spontaneous reports of reactions to MDMA, muscle tightness (jaw), anxiety, decreased appetite, headache, and fatigue were most commonly reported acutely during MDMA-assisted psychotherapy. During the week following treatment, the most frequently reported reactions were anxiety, fatigue, insomnia, depressed mood, and hypersomnia. The half-life of MDMA doses used in these studies is 8 to 9 hours and the majority of AEs have been transient, resolving within 2 to 3 days after MDMA has been metabolized and excreted. Severe anxiety, insomnia, fatigue, nausea, muscle tightness, and depressed mood are commonly reported in PTSD studies supported by the sponsor. These reactions also overlap with symptoms of pre-existing conditions in medical history associated with PTSD (depression, somatic symptoms, insomnia, anxiety), which may influence the reaction frequency observed during clinical trials of MDMA-assisted psychotherapy.

5.3.1 Reproductive and Developmental

All research studies with MDMA, with and without sponsor support, require measures to limit pregnancy risk prior to receiving each dose of MDMA. Women of childbearing potential must

use an effective method of birth control to be enrolled in sponsor-supported studies, and pregnancy tests must be negative prior to each experimental session. There is no information on reproductive and developmental risks reported as there have been no pregnancies in these studies. See Section 4.4.5 Reproductive and Developmental Toxicity for information gathered on reproductive and developmental risks in Ecstasy users.

5.3.2 Immunological Effects

Various groups have studied immunological effects of MDMA in laboratory settings, with none found to be clinically significant from a safety standpoint. Studies in men conducted by researchers in Spain have found 100 mg MDMA to have immunosuppressive and anti-inflammatory effects [117, 557, 575, 578, 579]. Findings included a decline in CD4 cells, smaller CD4/CD8 ratio, attenuated lymphocyte proliferation in response to mitogen, and an increase in natural killer (NK) cells, with effects diminishing but still detectable 24 hours after drug administration. These researchers also found that MDMA decreased production of pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and INF-γ, and increased production of anti-inflammatory cytokines, including IL-10 and TGF-ß. Generally, MDMA appeared to decrease the concentration of Th1 cytokines, including IL-2, and increase the amount of Th2 cytokines, including IL-4, measured in blood. Changes of similar magnitude and duration have been previously noted after ingestion of other psychoactive agents, such as alcohol or cocaine [117, 579]. Due to their limited duration, these changes are not likely to have clinical significance beyond several days of possible increased risk of viral upper respiratory infection or similar illness. Interestingly, meta-analysis and meta-regression of 20 studies investigating inflammatory markers in PTSD found an association with increased IL-6, IL-1β, TNF-α, and INF-γ, consistent with chronic low-grade inflammation [184], and any effects of MDMA on these immune markers remains to be tested.

Immunological changes seen after an initial dose of MDMA are enhanced by a second dose of identical size given 4 hours after the first dose [575, 580]. A second dose of identical size given 24 hours after the first dose produced the same immunological effects over the same time course, but with greater intensity than after the first dose [575]. Given this data, it is possible that administering a smaller supplemental dose 1.5 to 2.5 hours after the first dose will slightly enhance the immunological effects set in motion by the initial dose of MDMA. Previous Phase 1 studies mentioned above have not reported any indication of increased risk of illness occurring after MDMA administration.

5.3.3 Thermoregulatory Effects

In the first Phase 1 safety study funded by the sponsor, MDMA was found to cause a significant increase in body temperature in some healthy volunteers [47]. However, these increases were found to be transient and tolerable in a controlled clinical setting. Doses between 1.5 and 2 mg/kg produced only a slight elevation in body temperature that was not clinically significant [10, 556, 559] and this elevation was unaffected by ambient temperature [195]. Studies in MDMA-experienced volunteers given 2 mg/kg MDMA produced slight but statistically significant increases in core body temperature, at mean elevation of 0.6°C [195]. The same study found that ambient temperatures did not affect elevation in core temperature after administration of MDMA, which increased metabolic rate. A supplemental dose twice as large as the initial dose of MDMA elevates body temperature, but not beyond what would be expected after the cumulative dose [328]. While MDMA did not increase or decrease perspiration overall in this study, it was associated with a higher core temperature when perspiration began. Ambient temperature neither attenuated nor amplified the subjective effects of MDMA, with people reporting similar drug effects in warm and cool environments. As expected, people felt warm when the room was warm

and cold when the ambient temperature was cool, and MDMA did not distort perceptions of warmth or cold in either case. Unlike rodents given MDMA at higher mg/kg doses, humans do not exhibit reduced temperature when MDMA is given in a cold environment, and they do not exhibit significant hyperthermia in a warm environment. When compared with placebo, findings from 74 subjects given MDMA found that men exhibited a greater elevation in body temperature than women when given the dose of MDMA in mg/kg [10]. Subsequent studies have not confirmed this gender difference [26], and a report in a sample of 17 men and women reported higher oral temperatures in women [552]. A review of clinical placebo-controlled laboratory studies conducted without sponsor support found that route of measurement has an effect on variability in body temperature findings, with oral and tympanic, but not axillary, temperatures frequently rising above 38°C into moderate hyperthermia ranges at 125 mg MDMA [581]. Thermogenic effects of MDMA are distinct from malignant hyperthermia and are mediated by noradrenergic signaling, which contributes to peripheral effects of MDMA by affecting cutaneous vasoconstriction of blood flow and stimulation of heat production, and are attenuated by norepinephrine blocking drugs [582]. It is notable that subjects in studies in a clinical setting have not engaged in vigorous exercise and have remained either sitting or lying down throughout duration of drug effects. It may be the case that heat dissipation impaired by a hot environment, heat generation increased by exertion, interactions of serotonergic drugs, and potential disturbance of central heat regulation mechanisms contribute to the occurrence of hyperprexia (body temperatures >41°C) in people ingesting Ecstasy in uncontrolled settings. However, one of four naturalistic studies reported that Ecstasy users had a statistically significant increase in body temperature [583], while three others failed to find significant differences in Ecstasy-user body temperature at a club [584-586].

In all sponsor-supported studies to date, oral body temperature readings were taken at baseline, then every 60 to 90 minutes, with some differences in collection methods across studies. Peak values during each experimental session are ascertainable for all studies. Across studies, the final value was either at a relatively set time (MP-8, MP-12, MP1-E2) or as the final reading with time point varying (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and these were averaged. Average post-drug values serve as the final value for MP-2. If body temperature rose 1°C above the pre-drug reading, each duration above the pre-determined cut-off was collected in MP-2, MP-8, MP-12, MP-9, MP-4, MP1-E2, MAA-1, and MDA-1. Clinical signs and symptoms were monitored and more frequent readings were collected in cases where readings were above cut-off. Data presented below is final for completed studies and preliminary for ongoing studies.

Table 3: Pre-Drug, Peak, and Final Body Temperature During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies Across Populations

Dose	Subjects (Observation)	Pre-drug Min/Max Mean (SD)	Peak Min/Max Mean (SD)	Final Min/Max Mean (SD)	Subjects with BT Above Cut-off (Observations)
0 mg	14 (27)	35.1/37.2 36.4 (0.5)	36.4/37.6 36.9 (0.3)	35.9/37.5 36.6 (0.3)	2 (2)
25 mg	8 (18)	35.8/37.1 36.5 (0.3)	36.0/38.5 37.2 (0.8)	36.0/38.0 36.9 (0.7)	4 (6)
30 mg	7 (15)	35.3/36.9 36.3 (0.5)	36.4/37.9 37.0 (0.4)	35.7/37.2 36.5 (0.4)	4 (6)
40 mg	7 (12)	35.6/37.2 36.4 (0.5)	36.6/37.6 37.1 (0.3)	36.5/37.6 37.0 (0.4)	3 (3)
75 mg	13 (20)	35.9/37.8 36.6 (0.4)	36.3/37.8 37.2 (0.5)	36.1/37.6 36.8 (0.4)	2 (2)
100 mg	25 (42)	33.9/37.5 36.1 (0.8)	35.5/37.9 37.0 (0.47)	34.8/38.0 36.7 (0.7)	8 (12)
125 mg	95 (232) [A]	34.3/37.7 36.5 (0.5) [B]	36.0/38.7 37.3 (0.5)	35.2/38.4 36.9 (0.5)	50 (83)
150 mg	3 (4)	36.6/36.7 36.7 (0.1)	37.3/38.2 37.7 (0.4)	36.8/37.7 37.3 (0.4)	1 (2)

[A] One endpoint temperature was excluded pending queries, and two listings are unavailable for endpoint temperature.
[B] One subject given 125 mg did not have pre-dose values for any vital sign, but post-drug values were collected.

Based on the literature, MDMA is expected to produce elevations in body temperature with possible influence of ambient temperature. Body temperature above 1°C above baseline was detected in 33% (114 of 343) of experimental sessions where MDMA was administered at any dose, and in 46% (72 of 157) of subjects in sponsor-supported trials. Maximum body temperature observed to date was 38.7°C in one MP-2 subject lasting 3 hours, where 125 mg MDMA was administered as the initial dose. This subject had no risk factors reported in medical history and temperature elevation was not clinically significant. Maximum duration above 1°C elevation was 9.2 hours in one MP-9 subject where 125 mg MDMA was administered as the initial dose. This subject experienced a maximum of 38.0°C temperature, which dropped to 37.6°C at final reading. By contrast, elevation of body temperature above 1°C was observed in 7% (2 of 27) of experimental sessions and in 14% (2 of 14) of subjects receiving inactive placebo. Perspiration was reported in 21% to 25% of experimental sessions with active dose MDMA, and was generally mild. Adjustments were made to the ambient temperature and to air circulation in the room, but no subjects required medical intervention to decrease body temperature, and values returned to baseline as drug effects waned. In conclusion, controlled setting for treatments with MDMA-assisted psychotherapy are optimized with the capacity to control ambient temperature for subject comfort, though there is no evidence that this will significantly influence or is needed for control of core body temperature.

5.3.4 Cardiovascular Effects

MDMA produces sympathomimetic effects that include elevation in blood pressure and heart rate, first recorded by Downing [44] and replicated by other research teams in the U.S. and Europe [9, 10, 45]. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [7, 12, 26, 46]. Most people do not experience elevations that are greater than those seen after moderate

exercise. MDMA has also been found to decrease respiratory sinus arrhythmia, the natural variation in heart rate over the course of each respiratory cycle [587]. Cardiovascular effects of MDMA first appear 30 to 45 minutes after administration [44] and peak between 1 and 2 hours post-drug [11, 45], with effects waning 3 to 5 hours after drug administration. Men given the same mg/kg dose of MDMA as women exhibited a significantly greater elevation in blood pressure and heart rate in a study summarizing and pooling data from a series of human MDMA studies [10]. These studies did not report any discomfort or increased distress accompanying cardiovascular effects.

Elevation in blood pressure above 140/90 occurred in approximately 5% of research subjects receiving a single dose of at least 100 mg of MDMA in Phase 1 research studies [9, 13]. Peiro and colleagues observed elevation in blood pressure above 150/90 as well in all 10 subjects given 50 mg followed 2 hours later by 100 mg MDMA [328]. When compared with 100 mg MDMA and placebo given 4 hours apart, two doses of 100 mg 4 hours apart significantly elevated SBP, while other physiological were not significantly elevated beyond values seen after a single dose. These studies used different dosing regimens than the one used in sponsor-supported studies, which employ an optional supplemental half dose. None of these individuals needed clinical intervention and blood pressure returned to normal as drug effects waned [9, 13, 328].

Greater elevations in blood pressure are seen in individuals with a specific COMT genotype (Val158/Met genotype), and greater elevations in blood pressure and heart rate are seen in individuals with a specific SERT (l/* 5-HTTLPR) genotype [552]. However, the observed increases are not so severe as to suggest contraindication for these genotypes. The α_1- and beta-adrenergic receptor antagonist carvedilol is capable of reducing MDMA-induced elevations in blood pressure, heart rate, and body temperature when administered 1 hour before MDMA without affecting the subjective effects of MDMA, indicating the norepinephrine release is primarily responsible for cardiovascular effects of MDMA [207]. Other concomitant antihypertensive medications either alter some of the effects of MDMA [588] or do not significantly reduce MDMA-induced blood pressure elevation [205].

Norepinephrine release induced by MDMA leads to indirect activation of the AVP system, stimulating secretion of copeptin (CTproAVP), a 39-aminoacid glycopeptide that is a C-terminal part of the precursor pre-proAVP. CTproAVP is secreted into circulation from the posterior pituitary gland in equimolar amounts with AVP. CTproAVP directly reflects AVP concentration and can be used as a surrogate biomarker of AVP secretion. In many studies CTproAVP behavior represents changes in plasma osmolality, stress and various disease states (diabetes, SIADH, heart failure, renal disorders), and is an indicator of osmoregulatory function in the body [365]. Heart failure is commonly associated with hyponatremia, and is also characterized by increased concentrations of basal AVP and CTproAVP [375]. Intra-cardiac pressures, intra-arterial pressures, angiotensin II, pain, and adrenergic (α_2) central nervous stimuli can also influence AVP secretion [364]. Increased CTproAVP concentration is described in several studies as a strong predictor of mortality in patients with chronic heart failure and acute heart failure. [365]. Taken together, the AVP system appears to be the main connection between MDMA and cardiovascular risk as well as hyponatremia.

In all sponsor-supported studies to date, blood pressure readings were taken at baseline, with study-specific differences in data collection times post-drug. Peak values during each experimental session are ascertainable for all studies. The final or endpoint was recorded as the final value, either at a relatively set time (MP-8, MP-12, MP1-E2) or as the final value available, or with timepoint varying (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and these were averaged, whereas all other studies reported single time point pre-drug. Average post-drug values serve as the final value for MP-2. If SBP rose above

160 mmHg or if diastolic blood pressure (DBP) rose above 110 mmHg, each duration above this pre-determined cut-off for more frequent measurement was collected in MP-8, MP-12, MP-9, MP-4, and MP1-E2. In MAA-1, if SBP rose above 180 mmHg or if DBP rose above 110 mmHg, each duration above the pre-determined cut-off was collected. If SBP rose above 180 mmHg and if DBP rose above 120 mmHg, each duration above the pre-determined cut-off is collected in MDA-1. MP-2 criteria for cut-off was exceeding both 160/110 mmHg. Clinical signs and symptoms were monitored and more frequent readings were collected in cases where readings were above cut-off. Data presented below is final for completed studies and preliminary for ongoing studies.

Table 4: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies Across Populations

Dose	Subjects (Observations)	Pre-drug Min/Max Mean (SD)	Peak Min/Max Mean (SD)	Final Min/Max Mean (SD)	Subjects with SBP Above Cut-off (Observations)
0 mg	14 (27)	90/139 118.8 (13.0)	102/159 134.5 (16.3)	83/138 115.2 (13.5)	0
25 mg	8 (18)	110/130 119.9 (5.2)	117/147 133.6 (8.1)	107 /146 119.8 (11.3)	0
30 mg	7 (15)	94/134 114.2 (12.1)	110/155 132.3 (14.0)	98/140 118.5 (11.6)	0
40 mg	7 (12)	100/154 125.9 (14.1)	112/168 137.1 (17.7)	107/148 124.3 (12.1)	2 (2)
75 mg	13 (20)	101/145 124.2 (11.3)	116/179 144.7 (17.5)	107/156 127.8 (12.8)	3 (4)
100 mg	25 (42)	92/155 118.0 (13.4)	100/193 138.2 (22.8)	86/148 119.1 (14.6)	6 (8)
125 mg	94 (232) [A]	95/177 125.3 (14.9)	114/200 152.8 (17.4)	77/170 126.2 (15.7)	43 (78)
150 mg	3 (4)	102/146 128.0 (21.0)	128/185 156.5 (23.3)	117/161 141.0 (19.0)	1 (1)

[A] One subject given 125 mg did not have pre-dose values for any vital sign, but post-drug values were collected.

As described above, MDMA is expected to produce statistically significant but transient, self-limited increases in blood pressure. The supplemental half dose, when administered 1.5 to 2.5 hours after the initial dose, may cause further SBP increases above those resulting from the initial dose of MDMA. In one study (MP-1), 9 of 23 subjects received the supplemental dose, with four in the 125 mg MDMA group, in all subsequent studies, most of the subjects received the optional supplemental dose. A comparison of subjects receiving the supplemental dose to those who only received the initial dose in MP-1 indicate that the supplemental dose did not cause further elevation in blood pressure and heart rate beyond the initial dose, although the sample was underpowered to detect a small effect. Maximum SBP observed to date was 200 mmHg in a single MP-2 subject, lasting 5 hours, where 125 mg MDMA was administered as the initial dose. This subject had a medical history of controlled hypertension, and the traumatic event that caused PTSD was medical malpractice, with a secondary diagnosis of white coat hypertension. This subject was only enrolled after 24-hour monitoring of blood pressure at baseline to confirm this diagnosis. SBP above cut-off was detected in 27% (93 of 343) of experimental sessions where MDMA was administered, and in 35% (55 of 157) of subjects receiving MDMA in sponsor-supported trials. Maximum duration above SBP cut-off was 6 hours in two separate subjects with respective peak values of 172 and 174, where 125 mg MDMA was administered as the initial dose. Doses of 40 mg MDMA and greater were associated with elevations above cut-off. SBP

was elevated in 46% (43 of 94) of subjects and 34% (78 of 232) of experimental sessions where the 125 mg dose was administered. This was not observed in any of the sessions where inactive placebo or 25 mg to 30 mg MDMA was administered, supporting a dose dependent effect of MDMA on blood pressure. Despite elevations in SBP, no clinical signs or symptoms of hypertension were observed. In all cases, final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Table 5: Pre-drug, Peak, and Final Systolic Blood Pressure During Experimental Sessions in Controlled Hypertension Subjects in MAPS-Sponsored PTSD Study MP-8

Dose	Subjects (Observations)	Pre-drug Min/Max Mean (SD)	Peak Min/Max Mean (SD)	Final Min/Max Mean (SD)	Subjects with SBP Above Cut-off (Observations)
30 mg	1 (1)	125/125 125	131/131 131	124/124 124	0
75 mg	1 (2) [A]	133/145 139.0 (8.5)	170/179 174.5 (6.4)	147/147 147 (0)	1 (2)
100 mg	1 (3) [A]	122/140 132.0 (9.2)	179/193 185.0 (7.2)	133/147 140.7 (7.1)	1 (3)
125 mg	2 (6)	124/171 137.2 (18.8)	144/177 160.0 (14.0)	126/158 134.3 (13.9)	2 (3)

[A] The same subject received these doses of MDMA in different stages of the study.

Candidates with hypertension are excluded from participation in all but one of sponsor-supported studies to limit cardiovascular risk during treatments. In MP-8, four subjects with hypertension controlled by medications were permitted to enroll after completion of carotid ultrasound and nuclear exercise test (per protocol) in addition to usual medical screening for the study. Results are depicted above. One subject dropped out after receiving a single experimental session with 30 mg MDMA and did not experience SBP above cut-off. SBP above cut-off was detected in 75% (3 of 4) of subjects and 67% (8 of 12) of experimental sessions where MDMA was administered to this sub-group. The prevalence of these elevations appears higher in this sub-group than the overall sample, although the prevalence could decrease in a larger group. Pre-drug SBP was typically higher in this sub-group, and peak SBP of these subjects was typically at the upper end of the range of the overall sample. Final SBP readings remained 11 to 14 mmHg higher on average than pre-drug SBP readings in the subject who received 75 mg of MDMA in two blinded experimental sessions and 100 mg in three open-label crossover experimental sessions. However, two subjects receiving 125 mg MDMA had final readings that returned to pre-drug values, suggesting this could be an individual case with a medical history of both hypertension and hyperlipidemia. None of the subjects with controlled hypertension experienced AEs of the cardiovascular system.

Table 6: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies Across Populations

Dose	Subjects (Observations)	Pre-drug Min/Max Mean (SD)	Peak Min/Max Mean (SD)	Final Min/Max Mean (SD)	Subjects with DBP Above Cut-off (Observations)
0 mg	14 (27)	56.5/94 74.6 (9.1)	65/103 84.5 (10.2)	48/100 70.85 (10.9)	0
25 mg	8 (18)	59/84 73.9 (6.2)	76/92 83.2 (5.0)	63/81 72.33 (5.3)	0
30 mg	7 (15)	60/87 74.3 (8.4)	75/99 85.5 (7.5)	68/91 76.7 (6.3)	0
40 mg	7 (12)	69/95 82.7 (8.3)	72/135 90.2 (16.7)	68/96 80.3 (9.4)	1 (1)
75 mg	13 (20)	56/95 75.1 (10.1)	73/118 88.6 (11.2)	59/100 76.1 (10.2)	2 (3)
100 mg	25 (42)	52/93 74.1 (10.6)	62/125 86.9 (15.2)	58/99 74.6 (10.0)	2 (4)
125 mg	95 (232)	54/120 79.1 (9.9)	69/126 92.5 (9.6)	53/104 78.2 (9.8)	6 (8)
150 mg	3 (4)	60/90 78.8 (14.0)	78/108 95.3 (12.6)	67/96 82.0 (12.2)	0

DBP exceeded cut-off in only 5% (16 of 343) of experimental sessions and in 7% (11 of 157) of subjects at any MDMA dose. Maximum duration above DBP cut-off was 5 hours in MP-2 subject 112, with a peak of 114, where 125 mg MDMA was administered as the initial dose. This subject had a high pre-drug DBP reading of 96, and also experienced the highest SBP in sponsor-supported studies to date, as described above. In contrast, 14 subjects participating in 27 experimental sessions with placebo did not experience any elevations in blood pressure above cut-off. In experimental sessions with 25 mg to 30 mg MDMA, elevations in blood pressure above cut-off were not observed either, supporting a dose-dependent effect of MDMA on blood pressure. In all cases, final values returned to pre-drug levels with no clinical intervention required. No clinically significant AEs were reported based on elevations in blood pressure.

Table 7: Pre-drug, Peak, and Final Diastolic Blood Pressure During Experimental Sessions in Controlled Hypertension Subjects in MAPS-Sponsored PTSD Study MP-8

Dose	Subjects (Observations)	Pre-drug Min/Max Mean (SD)	Peak Min/Max Mean (SD)	Final Min/Max Mean (SD)	Subjects with DBP Above Cut-off (Observations)
30 mg	1 (1)	85/85 85	86/86 86	77/77 77	0
75 mg	1 (2) [A]	89/95 92 (4.2)	113/118 115.5 (1.8)	91/100 95.5 (6.4)	1 (2)
100 mg	1 (3) [A]	77/91 83.7 (7.0)	121/125 123.0 (2.0)	82/99 90.7 (8.5)	1 (3)
125 mg	2 (6)	82/101 87.8 (8.4)	91/110 98.5 (7.5)	84/93 86.0 (7.5)	0 (0)

[A] The same subject received these doses of MDMA in different stages of the study.

DBP above cut-off was detected in one of four subjects (25%) and five of 12 (41%) of experimental sessions where MDMA was administered at any dose to subjects with controlled

hypertension. All five cases were in the same subject, who received both 75 mg and 100 mg MDMA and is described above. Of all observations of DBP above cut-off across studies and populations, 31% (5 of 16) of experimental sessions were attributed to this subject, suggesting that pre-existing risk factors are associated with elevations in blood pressure. However, this subject did not experience any AEs of the cardiovascular system and DBP resolved back to baseline at final reading in all cases.

In all sponsor-supported studies to date, heart rate readings were taken at baseline, with study-specific differences in data collection times post-drug. Peak values during each experimental session are ascertainable for all studies. The final or endpoint value was recorded as the final value, either at a relatively set time (MP-8, MP-12, MP1-E2) or as the final value available, with time point varying (MP-1). MP-1 and MP-2 reported two pre-drug values (15 minutes and 5 minutes before dosing) and these were averaged, whereas all other studies reported single time point pre-drug. Average post-drug values serve as the final value for MP-2. If heart rate rose above 110 bpm, each duration above the pre-determined cut-off was collected in MP-8, MP-12, MP-9, MP-4, and MP1-E2. Duration of pulse above cut-off was not collected in MP-2. Clinical signs and symptoms were monitored and more frequent readings were collected in cases where readings were above cut-off.

Table 8: Pre-drug, Peak, and Final Heart Rate During Experimental Sessions with Placebo or any MDMA Dose in MAPS-Sponsored Studies Across Populations

Dose	Subjects (Observations)	Pre-drug Min/Max Mean (SD)	Peak Min/Max Mean (SD)	Final Min/Max Mean (SD)	Subjects with HR Above Cut-off (Observations)
0 mg	14 (27)	45/111 69.9 (16.3)	54/108 81.2 (14.0)	45/92 70.7 (11.8)	0
25 mg	8 (18)	45/94 69.9 (13.7)	50/124 84.1 (19.8)	51/90 71.7 (12.3)	0
30 mg	7 (15)	45/91 67.1 (14.6)	54/102 81.1 (16.0)	50/89 72.7 (13.0)	0
40 mg	7 (12)	66/110 80.8 (14.3)	69/126 90.7 (15.6)	56/120 83.4 (18.7)	1(1)
75 mg	13 (20)	54/85 72.2 (8.8)	58/123 93.2 (16.9)	57/102 80.9 (13.2)	2 (4)
100 mg	25 (42)	42/114 68.5 (13.5)	63/139 96.6 (17.5)	55/103 78.6 (11.7)	6 (10)
125 mg [A]	95 (232)	36/122 74.9 (13.9)	63/160 104.7 (18.07)	47/135 85.0 (15.1)	51 (90)
150 mg	3 (4)	69/96 79.3 (11.7)	83/125 105.8 (17.3)	74/112 94.5 (15.8)	1 (1)

[A] A single value was not recorded for final readings in subjects receiving 125 mg.

Heart rate elevation above the pre-determined cut-off was detected in 31% (106 of 343) experimental sessions at any MDMA dose, and in 39% (61 of 157) of subjects receiving MDMA. Maximum peak pulse was 160 bpm reported in a subject who received 125 mg MDMA, with pulse remaining above cut-off for 60 minutes. At final reading 3.75 hours later, pulse had returned to below cut-off levels of 93 bpm. The maximum duration above cut-off was 9.5 hours in MP-1 subject 218, were 125 mg MDMA was administered as the initial dose. This subject experienced a peak pulse of 121, which dropped at final reading to 119. Subject 218 had no cardiovascular risk factors in medical history. In cases where blood pressure or heart rate was above cut-off, vitals were monitored more frequently. No subjects receiving MDMA in sponsor-

supported clinical trials have required any clinical interventions for elevated blood pressure or pulse, as all values returned to normal as the effects of MDMA diminished.

The values presented above suggest a dose-dependent action on SBP and heart rate, which is supported in the literature in healthy controls [7, 9, 12, 589]. Peak body temperature and values above cut-off do not appear to be strongly related to MDMA dose, with values above cut-off occurring at every dose, including inactive placebo. While peak DBP is higher after doses of 100 mg or greater, very few reports of DBP elevated above cut-off occurred during MDMA administration, suggesting that this is a less common response than elevated SBP or pulse.

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

Vital signs for subjects in the study of social anxiety in people on the autism spectrum appear to be similar to those made in people with PTSD receiving equivalent doses of MDMA. Only one measurement rose above pre-determined cut-off values in this sample (pulse above 110, for approximately 1 hour). Comparatively small sample size and use of somewhat lower doses may explain this difference. Differences in age may be involved, with the average age of MAA-1 subjects examined in the IB being 30.65, while mean age in PTSD studies is in the early to mid-40s [43, 590]. No subjects in this study have required any medical interventions.

5.3.5 Osmoregulatory Effects

The neuroendocrine hormone copeptin, described in Section 5.3.4 Cardiovascular Effects as correlating with AVP in blood, was detected in women acutely after 125 mg MDMA administration [561], and this finding was reproduced in another study reporting that 47.5 mg MDMA caused an acute rise in AVP and a small decrease in plasma sodium, at a time of day when it would not be expected to change, in an all-male sample. [251]. The sponsor-supported study MAA-1 includes AVP assessments in peripheral plasma samples before, during, and after MDMA-assisted psychotherapy. This study is ongoing and results are pending analysis.

5.3.6 Hepatic Effects

The first two sponsor-supported Phase 2 studies (MP-1, MP-2) assessed liver function after completion of two or three blinded experimental sessions. Values that differ from established, age-appropriate norms were evaluated for clinical significance. Laboratory assessments of liver function were not conducted after experimental sessions in subsequent sponsor-supported studies and no AEs related to liver function have been reported in these studies.

Table 9: List of All Clinically Significant Changes in Laboratory Values in Two Subjects from MP-2

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

Two subjects in the MP-2 study reported two clinically significant abnormalities. One was an elevation in bilirubin in a subject with a family history of elevated bilirubin (probably Gilbert's

syndrome), with the elevation occurring after open-label treatment with 125 mg to 150 mg initial dose of MDMA. Bilirubin levels can be indicative of decreased liver function, but the liver enzymes were normal at that time, supporting the interpretation that the bilirubin levels were slightly elevated compared to baseline due to hereditary factors. The other abnormal laboratory value, an elevation in erythrocyte sedimentation rate (ESR), a marker of inflammation, occurred in a subject with a medical history of breast cancer. This value was recorded 3 months after the last administration of MDMA as an AE unrelated to the study drug.

Table 10: Average ALT Values at Baseline and 2-Month Follow-up After Two Experimental Sessions in Subjects from MP-1

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

[A] ALT value for one subject not recorded at baseline.

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

5.3.7 Neurobiological Effects

Early investigations in healthy volunteers used PET to detect changes of brain activity after MDMA and found decreased left amygdalar activity and increased frontal activity [28]. PET brain scans 75 minutes after administration of 1.7 mg/kg MDMA found increased regional cerebral blood flow (rCBF) in ventromedial prefrontal, inferior temporal, and cerebellar areas and decreased rCBF in the left amygdala [28]. In a different study, arterial spin labeling has also found decreased cerebral blood flow (CBF) in the right amygdala and hippocampus after MDMA administration [27]. The decreased CBF correlated with drug intensity ratings after 100 mg MDMA. Blood oxygen level dependent (BOLD) MRI scans of resting-state functional connectivity in the same sample detected complementary decreases in medial PFC-hippocampal coupling and increases in right amygdala-hippocampal coupling, although the relationship did not achieve statistical significance [27]. Decreased activity in the amygdala may be indicative of reduced reactions to potential threats [591]. MDMA (100 mg) increased subjective ratings of positive mood in response to positive memories and decreased negative response to negative memories. Attenuated activity in the left anterior temporal area was detected after MDMA during worst memory recall. [36].

During a task that required keeping a visual target cue in mind, visual attention, and response inhibition, brain imaging detected changes in parietal activity after 75 mg MDMA compared with placebo [576]. MDMA increased activity in frontal areas and decreased activity in occipital sites as measured via functional MRI (fMRI) [592]. Reduced resting-state cerebral blood flow in right amygdala and hippocampus after MDMA was associated with greater intensity of self-reported subjective effects [27]. Subjects given MDMA exhibited similar brain activity when reading or encoding a word list, suggesting that they were investing similar effort into both tasks. Ten Ecstasy user subjects receiving a minimum of two doses of 1 to 1.25 mg/kg or 2.25 to 2.5 mg/kg

MDMA exhibited signal decreases in bilateral visual cortex, caudate, superior parietal, and dorsolateral frontal regions 10 to 21 days later, with increased rCBF measured in two subjects at a later time point. However, a comparison between heavy Ecstasy users and non-user controls failed to find differences in baseline rCBF [593], and a report assessing changes before and after initial Ecstasy use found increased rCBF in only one area of the prefrontal cortex [266], suggesting that the changes seen by Chang and colleagues are a transient effect. EEG recorded 2 hours after MDMA administration showed the following changes in EEG activity: overall increase in beta activity, reduction in alpha activity, localized decreases in alpha and delta in frontal areas, and increased frontotemporal beta signal [594]. The authors reported the EEG patterns after MDMA were similar to those seen with serotonergic and noradrenergic drugs, as well as, but to a lesser extent, dopaminergic drugs.

The sponsor is undertaking a small BOLD fMRI pilot study investigating brain activity in people with PTSD before and after MDMA-assisted psychotherapy, as a substudy of a sample of people enrolled in MP-8. Brain activity is recorded while the subject is listening to a neutral and a personalized trauma-related scripts. Preliminary findings are pending analysis.

Monoamine neurotransmitters are known to modulate sleep architecture and alertness. In a trial with 2 mg/kg MDMA given 6 hours prior to preparing for sleep, MDMA was found to increase Stage 1 sleep and produce fewer periods of REM sleep without increasing daytime sleepiness [281]. Sample size of seven in this study suggests that findings should be accepted with caution. PTSD patients suffer from poor sleep quality. Disturbed REM or non-REM sleep is a contributing factor to maladaptive stress and trauma responses and chronic sleep disruption associated with nightmares caused by PTSD may be an indicator of efficacy of PTSD treatments. The sponsor is collecting secondary outcomes in PTSD studies with the Pittsburg Sleep Quality Index. Results are pending analysis from ongoing studies.

5.3.8 Neuropsychological Effects

MDMA alters mood, perception, and cognition in healthy volunteers, with effects on emotion and social behavior. At doses of at least 1 mg/kg (approximately 70 mg) and higher, active doses of MDMA alter mood and cognition, and produce slight alterations in perception [10, 529]. Acute subjective effects peak 90 to 120 minutes after oral administration and return to pre-drug levels 3 to 6 hours later [13, 595, 596]. Sub-acute effects assessed in controlled and naturalistic studies may occur 1 to 3 days after drug administration, but are no longer apparent seven to 14 days later [12, 324, 597]. Most of the therapeutic effects of MDMA are thought to result from changes in affect, cognition, and social interaction.

At least four research teams published relevant findings in studies of healthy volunteers during 2013 and 2014, examining the effects of MDMA on social cognition with several experimental paradigms assessing brain activity during episodic memory recall and assessing contributions of oxytocin and cortisol to the acute effects of MDMA. Findings include reduced reactivity to simulated social exclusion, reduced negative emotional response to self-selected "worst" memories, increased use of language related to interpersonal closeness, increased emotional empathy and increases in perceived partner empathy. One study reported greater social language after MDMA than with the psychostimulant methamphetamine [37], and another reported greater emotional empathy after MDMA and another psychostimulant, methylphenidate [34]. Taken together, this research lends greater support to the view that MDMA possesses unique psychological effects, distinct from psychostimulants that can be beneficial when combined with psychotherapy. As an entactogen, MDMA can promote increased trust, greater ability to face and cope with emotionally distressing memories, thoughts or feelings and greater emotional empathy toward the self as well as others.

When combined with psychotherapy, MDMA permits people to confront and consider emotionally intense memories, thoughts, or feelings, and perhaps through changes in mood and perception, increase empathy and compassion for others and oneself [41, 62, 527]. In a sub-study of MP-8, the Self Compassion Scale [598] was administered before and 2 months after MDMA-assisted psychotherapy. Preliminary results in this small sub-study (N=7) are trending upward; subjects were low in self-compassion with mean total score of 2.4±0.63 prior to the study and experienced an increase to moderate self-compassion with mean total score of 2.8±0.84. In this assessment, self-kindness and a sense of common humanity increased, while self-judgment and feelings of isolation decreased on average within-subjects.

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

5.3.8.1 Cognitive Function

MDMA does not affect responses on tasks requiring attention and response to visual stimuli or visually presented words [13, 28], but has been shown to interfere with performance on digit-symbol substitution, a measure of attention, psychomotor speed and visual memory [8]. A dose of 75 mg improved visual tracking speed, but impaired estimating the position of a blocked (occluded) object in a study of acute effects on skills used for driving cars [595]. A series of studies conducted in the Netherlands examined the effects of MDMA on skills needed for automobile driving reported transient and selective changes in verbal and visual attention, and memory after 75 or 100 mg MDMA [599-602]. MDMA caused difficulty learning or remembering lists of words and difficulty recalling object position within an array of objects. MDMA did not cause impairment in spotting scene changes and reduced weaving in a driving simulation. MDMA was associated with an excessively cautious response to the actions of another car in an assessment of actual driving [603]. While these studies have added to the literature of MDMA's cognitive effects, people in sponsor-supported studies are advised to never operate a vehicle while under the influence of MDMA or any other psychoactive substance.

MDMA acutely improved performance on one measure of impulsivity while failing to affect performance on other impulsivity measures [600]. The causes of these changes are unclear but may relate to changes in attention, salience of visual objects, and altered time perception. Changes in visuospatial recall and driving skills are likely associated with serotonin release or indirect action on serotonin receptors, as the noradrenergic and dopaminergic drug methylphenidate (Ritalin) did not produce similar changes [599, 602, 603]. A study on performance monitoring compared the effects of ethanol, MDMA, and both substances combined, found that MDMA had no effect on performance monitoring and no interaction when ethanol and MDMA are administered concurrently [604]. Administration of a $5HT_{2A}$ receptor antagonist, but not a $5HT_{1A}$ antagonist, reduced impaired performance on a word learning and recall task after MDMA, suggesting that interference is due in part to direct or indirect activation of these receptors [233]. Changes in cognitive function and psychomotor skills occurred during peak drug effects, but were not detectable 24 hours later.

Acute effects on cognitive function are not assessed in sponsor-supported studies. In three MAPS-sponsored studies, MP-1, MP-4, and MP-12, long-term effects on cognitive function was assessed by administering the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), a relatively brief measure that assesses memory, attention and processing speed, visual-spatial and constructional abilities, and expressive language [605]; and the Paced Auditory Serial Addition Task (PASAT), a measure of auditory processing speed and mental flexibility [606, 607]. These instruments were given prior to and 1 to 2 months after psychotherapy assisted with either MDMA or comparator or placebo.

In MP-1, no significant differences in cognitive function were detected at the 2-month follow-up between subjects who received two sessions with 125 mg of MDMA compared to subjects who received placebo, as measured by RBANS and PASAT [41]. These findings suggest that MDMA did not impair cognitive function in this sample or that the effect was too small to attain statistical significance in this small pilot study. Two ongoing studies (MP-12 and MP-4) include these measures to assess reproducibility of this finding. Since both MP-4 and MP-12 were ongoing as of the data cut-off, available data pooled across studies are presented below by dose.

Table 11: Neurocognitive Function - RBANS Mean Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12 as of 01 October 2015

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)	End of Stage 2 Mean (SD)
0 mg	100.9 (15.38) N=10	106.9 (15.15) N=10	---	119.0 N=1
40 mg	94.7 (5.20) N=6	102.0 (10.58) N=3	---	101.3 (5.51) N=3
100 mg	95.0 (17.87) N=6	104.9 (15.75) N=7	101.5 (18.97) N=6	---
125 mg	102.9 (15.88) N=27	103.1 (12.70) N=22	99.5 (9.33) N=6	---

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

Table 12: Neurocognitive Function - PASAT Trial 1 and Trial 2 Mean Raw Total Scores at Baseline, Primary Endpoint, End of Stage 1, and End of Stage 2 for MP-1, MP-4, and MP-12 as of 01 October 2015

PASAT Trial 1				
Dose	**Baseline Mean (SD)**	**Primary Endpoint Mean (SD)**	**End of Stage 1 Mean (SD)**	**End of Stage 2 Mean (SD)**
0 mg	42.1 (12.59) N=10	43.7 (12.03) N=10	---	37.0 N=1
40 mg	43.6 (10.36) N=5	53.3 (4.16) N=3	---	52.7 (5.03) N=3
100 mg	44.3 (12.44) N=6	46.7 (9.74) N=7	49.3 (9.09) N=6	---
125 mg	44.1 (11.12) N=27	49.1 (8.48) N=22	53.0 (6.36) N=6	---
PASAT Trial 2				
0 mg	34.2 (11.21) N=10	38.6 (11.66) N=10	---	45.0 N=1
40 mg	34.0 (13.36) N=5	43.0 (10.39) N=3	---	45.7 (8.15) N=3
100 mg	31.2 (12.67) N=6	29.0 (13.37) N=7	38.0 (10.33) N=6	---
125 mg	32.6 (9.62) N=27	35.4 (8.42) N=21	42.0 (11.8) N=6	---

On average, PASAT scores stay about the same after treatment with placebo and 100 mg initial dose of MDMA and trend towards improvement after treatment with 40 and 125 mg initial dose of MDMA. The trend towards improvement could be a practice effect from repeated assessments or could be correlated with PTSD symptom reduction. One to three additional treatments with open-label active dose MDMA do not appear to worsen cognitive function and continued to trend towards improvement on average based on preliminary End of Stage 1 and End of Stage 2 results. Cognitive function tests such as the PASAT are also known to be subject to individual variability, as they require basic proficiency with mathematical skills that are influenced by education level. The significance of these pooled findings is yet to be determined, but it does not appear that MDMA-assisted psychotherapy is negatively impacting cognitive function.

5.3.8.2 Perceptual Effects

MDMA causes slight changes in visual or auditory perception, including changes in the brightness or colors, sounds seeming closer or farther away, and simple visual distortions [7, 8, 10, 12]. Subjects also experienced altered time perception, and changes in meaning or significance of perceptions after MDMA [13]. On average, subjects maintained insight of their experience, with little indication that MDMA produces any strong alterations to the sense of self or control over the experience [11, 12]. Three healthy volunteers reported developing minimal to mild unusual beliefs or delusions under the influence of 1.5 mg/kg MDMA. Findings from a study with a small sample (five per group), perceptual alteration may be more pronounced after 2 mg versus 1 mg [596]. These beliefs resolved within a few hours, or by the next day at the latest. These subjects were aware that these beliefs were unusual [12]. Women reported experiencing all subjective effects of MDMA more intensely compared to men, but especially those related to perceptual changes [10]. The perceptual effects of MDMA appear to be the result of direct or indirect action on $5HT_{2A}$ receptors, as co-administration of the $5HT_{2A}$ antagonist ketanserin reduced reported perceptual alterations, as well as eliminated slight elevations in body temperature after 1.5 mg/kg MDMA [559], while co-administration with the $5HT_{1A}$ antagonist

pindolol did not affect perceptual alteration [231]. The effects of MDMA upon perception have not been studied within sponsor-supported studies.

5.3.8.3 Social Effects

In controlled laboratory settings, an established measure of accurate facial expression reading found that MDMA improved detection of expressions of positive mood and reduced accuracy in detecting expressions of negative mood [30]. Despite initial findings in naturalistic studies suggesting that Ecstasy increased accuracy of assessing some emotional expressions, particularly fearful ones [608], an fMRI study found that 0.75 and 1.5 mg/kg MDMA reduced signaling in the amygdala in response to angry faces when compared with placebo without changing the response to faces showing fear [26]. These researchers also detected increased activity in the ventral striatum in response to happy faces. Taken together, these findings suggest that MDMA changes the way emotional facial expressions are processed or the response to them. Complementing these findings are results demonstrating that MDMA enhanced the accuracy of recognizing facial expressions of positive mood and impaired mind reading for facial expressions of negative mood, but had no effect on mind reading for neutral faces [30]. Enhanced mind reading of positive emotions may facilitate therapeutic relationships in MDMA-assisted psychotherapeutic settings. In addition, and contrary to the finding in the early naturalistic study described above, there is some evidence showing that MDMA produces selective difficulty in recognizing faces expressing fear [588]. Further investigation corroborates this finding, showing that MDMA reduced recognition accuracy of fear significantly more in women than in men, and reduced recognition accuracy of sadness in women, but not in men. The same study found MDMA-induced increases in both implicit and explicit emotional empathy in men, but not in women [19].

Findings in placebo-controlled trials suggest that MDMA enhances positive response to positive social stimuli. Wardle and colleagues observe this effect simultaneously with a decrease in positive response to positive stimuli with no social content, which suggests that the contrast in valuation of social and non-social emotional stimuli contributes to MDMA's prosocial effects [38]. MDMA also reduces the impact of rejection on mood and self-esteem [609], which manifests more strikingly at lower doses of MDMA than reduction in perceived social rejection, suggesting complex social and behavioral effects from MDMA. Moreover, results from Kirkpatrick and colleagues show a behavioral preference for social activities over non-social ones, with subjects reporting increased desire for only the social activity after 1.5 mg/kg MDMA [610].

In a study by Bedi and colleagues, MDMA induced changes in semantic speech content with natural language learning software. Through natural language processing (NLP), researchers found speech patterns after MDMA were distinct from those produced after methamphetamine and placebo [37]. Proximity of speech to the concepts of *friend*, *support*, *intimacy*, *rapport*, and *empathy* was increased in the MDMA drug condition, which may bear some significance for the use of MDMA in therapy. MDMA did not affect the overall structure of subjects' speech. These findings were confirmed in an additional sample through a standardized dictionary method and machine learning, indicating that MDMA increased the use of social words, as well as words connoting positive and negative emotions [240]. There is some evidence that the increases in affiliative and prosocial feelings are separable from romantic or sexual feelings. Men and women did not seek to prolong viewing of images with explicit sexual content after MDMA, and they did not impute increased romantic feelings to images of heterosexual couples [611].

While the hormone oxytocin is implicated in social interactions and bonding, evidence indicates that oxytocin alone does not explain MDMA's prosocial effects. One investigation found a positive correlation in subjective effects ratings between intranasal oxytocin and oral MDMA, but

only at the lower of the two oxytocin doses tested [63]. Using pindolol to block 5-HT_{1A} receptor mediation of oxytocin's effects, Kuypers and colleagues determined that MDMA increased emotional empathy while oxytocin did not produce similar effects on measures of empathy and social interaction [569]. Studies examining the prosocial effects of MDMA, in relation to oxytocin, should be considered in the context of previous findings that showed no discernable subjective effects were found for intranasal oxytocin [612]. A single nucleotide polymorphism in the oxytocin receptor gene was found to predict subjective responses to MDMA, suggesting that this question remains worthy of further study [613]. Two studies have found that MDMA increased AVP [251, 561]. Neither study reported analysis or findings concerning any relationship between AVP levels and the subjective, emotional or social effects of MDMA.

Studies in healthy controls comparing doses between 0.75 and 1 mg/kg and 1.5 to 2 mg/kg suggest that the higher dose produces greater prosocial effects than the lower dose, while the lower dose may increase self-reported loneliness and use of empathy-related language [35, 39, 596, 609]. However, higher doses also produce a greater degree of stimulation and anxiety. It is notable that the first study investigating the impact of variation in an oxytocin receptor gene reported that those with one variation did not exhibit an increase in sociability after 1.5 mg/kg without a statistically significant difference in response at 0.75 mg/kg [613].

5.3.8.4 Emotional Effects

MDMA increases positive mood and anxiety [8, 10-12] on measures of alteration in consciousness and subjective effects. There is evidence that increases in positive mood and anxiety increase with dose [8, 12, 35, 614]. MDMA users report feeling more talkative and friendly after receiving MDMA. Self-reported interpersonal closeness was noted during a study in healthy volunteers [13]. Subsequent research confirmed the occurrence of increased interpersonal closeness after MDMA [29, 30, 35, 91, 558]. Researchers using two items within an instrument designed to assess drug effects and a visual analog scale rating closeness to others failed to detect increased feelings of empathy after 1.5 mg/kg MDMA [12], possibly due to the low sensitivity of these measures. In another investigation, the SSRI paroxetine was pre-administered to healthy volunteers before administering MDMA. The researchers found that MDMA increased feelings of being social and closeness to others, and paroxetine reduced these effects, indicating a significant role of the serotonergic system for the prosocial effects of MDMA [91]. People have reported feeling anxious or experiencing negative derealization while under the influence of MDMA, including increased anxiety related to loss of control and experiences of racing or blocked thoughts [8, 10, 13].

People receiving active doses of MDMA experience euphoria, positive mood, vigor, and positively experienced derealization, consonant with early retrospective reports, but also report experiencing anxiety, tension, and dysphoria, as well as concern over losing control over the self [8, 10-12]. More surprisingly, subjects report increased positive mood even after a dose of 25 mg [614]. It is uncertain whether the increases in positive and negative mood occur simultaneously or at different times throughout the duration of MDMA effects; evidence from two different teams suggests that peaks in negative mood may precede peaks in positive mood [11, 563]. MDMA may have a greater impact on mood in women than in men. Women report greater elevation in negative mood despite reaching plasma concentrations of MDMA and metabolites similar to those of men [552]. A second dose of MDMA 2 hours after the first does not increase subjective effects beyond that of an initial dose, interpreted by Peiro and colleagues as indications of tolerance to these effects [328]. When two 100 mg doses are given 4 hours apart, most subjective effects are comparable to those after a single dose, despite there being double the amount of plasma MDMA [546]. It is notable that the second dose in this study was identical to the first

dose, in contrast to sponsor-supported studies, wherein the second dose is half the size of the initial dose.

5.3.8.5 Suicidal Ideation, Behavior, and Depression

There is high incidence of positive suicidal ideation and behavior in populations of people with PTSD, especially those suffering from chronic, treatment-resistant PTSD [615, 616]. The FDA has responded to concerns over the occurrence of treatment emergent suicidal ideation or behavior by requiring clinical trials of psychiatric drugs to measure suicidality via the C-SSRS, a clinician-administered guided interview [617]. A score of 4 or 5 on the suicidal ideation category is considered serious, as well as a score of 1 or greater on the behavior category, and individuals with serious ideation or behavior are closely followed until levels return to normal or additional interventions are recommended. In order to determine if suicidal ideation and behavior worsens or improves after treatment in ongoing MAPS-sponsored trials (MP-4, MP-8, MP-9, MP-12, MAA-1, MDA-1, and MT-1), the C-SSRS is given repeatedly throughout a study, including lifetime incidence, baseline, before/during/after drug administration, endpoints when other measures are administered, and follow-up visits. Findings concerning suicidal ideation or behavior have not been formally measured in the first two sponsor-supported studies or reported in studies of healthy volunteers. Due to the nature of the therapeutic method, wherein a person may re-experience emotions associated with the traumatic event in order to reprocess the memory in a new, less detrimental way, thoughts of ending one's life may surface during this process. However, evidence from clinical studies indicates that these thoughts are most often transient, returning to normal, or even improve during the acute period following MDMA treatment. C-SSRS scores have also escalated during the preparatory sessions (before any drug administration), which is thought to be either a result of discussing traumatic experiences, or subjects tapering off long-prescribed medications, such as SSRIs and benzodiazepines, which have been documented elsewhere to induce suicidal ideation or behavior during withdrawal [618-620]. During both non-drug and MDMA-assisted psychotherapy sessions, subjects are asked to think about and discuss their experiences, thoughts, and emotions related to their condition. They may experience intense emotional responses to recalling and speaking about this material. As MDMA is only administered in combination with psychotherapy, the distress associated with psychotherapy is unavoidable, and is considered a necessary part of the therapeutic process that requires proper facilitation and support from therapists.

In Tables 13 through 17 below, suicidal ideation and behavior are summarized for subjects in MP-4, MP-8, MP-9, MP-12, MDA-1, and MAA-1 according to suggestions made in the C-SSRS Scoring and Data Analysis Guide [621]. A positive response for suicidal ideation is counted when a subject responds "yes" to any one of the five suicidal ideation questions (Categories 1 to 5) on the C-SSRS (i.e. a score >0 for suicidal ideation score). Serious suicidal ideation is a suicidal ideation score of 4 or 5. A positive response for suicidal behavior occurs when a subject responds "yes" to any one of the five suicidal behavior questions (Categories 6 to 10) on the C-SSRS (i.e. a score >0 for suicidal behavior score). Lifetime scores account for all suicidal ideation and behavior prior to enrollment according to subject recall and medical records. Pre-drug exposure represents measures collected on the Since Last Visit C-SSRS after enrollment during preparatory sessions and before first drug administration in experimental session 1 upon completion of tapering off psychiatric medications. Frequencies are event-based, calculated based on percentage of observations in which subjects would have the opportunity to report, as the C-SSRS is collected multiple times with each exposure to MDMA.

Table 13: Summary of Baseline Positive and Serious Responses on C-SSRS for Studies MP-4, MP-8, MP-9, MP-12, MAA-1, and MDA-1 as of 01 October 2015

Condition		Lifetime [A] N (%)	Pre-drug Exposure [B] N (%)
PTSD			
Blinded	PI	3 (75%)	3 (38%)
Placebo	SI	2 (50%)	0 (0)
(0 mg)	PB	2 (50%)	0 (0)
	O	4	8
	N	4	4
Blinded	PI	11 (79%)	5 (15%)
Comparator Doses	SI	3 (21%)	0 (0)
(25-40 mg)	PB	6 (43%)	0 (0)
	O	14	33
	N	14	13
Blinded	PI	41 (93%)	28 (29%)
Active Doses	SI	19 (43%)	0 (0)
(75-125 mg)	PB	19 (43%)	2 (2%)
	O	44	97
	N	44	44
Social Anxiety in Autistic Adults			
Blinded	PI	2 (100%)	0 (0)
Placebo	SI	0 (0)	0 (0)
(0 mg)	PB	1 (50%)	0 (0)
	O	2	3
	N	2	2
Blinded	PI	2 (100%)	0 (0)
Active Doses	SI	1 (50%)	0 (0)
(75-125 mg)	PB	1 (50%)	0 (0)
	O	2	6
	N	2	3
Anxiety Associated with a Life-threatening Illness			
Blinded	PI	1 (50%)	3 (38%)
Placebo	SI	1 (50%)	0 (0)
(0 mg)	PB	0 (0)	1 (13%)
	O	2	8
	N	2	2
Blinded	PI	1 (50%)	0 (0)
Active Dose	SI	0 (0)	0 (0)
(125 mg)	PB	1 (50%)	0 (0)
	O	2	8
	N	2	2

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

Based on lifetime results, most subjects across populations and dose groups had a history of suicidal ideation. In the PTSD sample, 39% of subjects had a history of serious ideation and 43% had positive behavior, which is consistent with the literature. Although samples were small, non-PTSD samples also have evidence of suicidal ideation and behavior, although prevalence may change as these studies enroll more subjects. Two PTSD subjects randomized to active dose and one autistic subject randomized to placebo exhibited suicidal behavior prior to any MDMA administration.

Table 14: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for Studies MP-4, MP-8, MP-9, and MP-12 as of 01 October 2015

Condition		Session 1 N (%)			Session 2 N (%)			Session 3 N (%)		
		Pre-drug [A]	During-drug [B]	Integration Day 1	Pre-drug [A]	During-drug [B]	Integration Day 1	Pre-drug [A]	During-drug [B]	Integration Day 1
PTSD										
Blinded	PI	1 (25%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	---	---	---
Placebo	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
(0 mg)	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
	N	4	4	4	4	4	4			
Blinded	PI	1 (7%)	1 (8%)	0 (0)	0 (0)	0 (0)	1 (8%)	1 (33%)	0 (0)	0 (0)
Comparator	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Doses	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
(25-40 mg)	N	14	13	13	12	11	12	3	2	2
Blinded	PI	9 (21%)	3 (7%)	5 (12%)	9 (21%)	7 (17%)	2 (5%)	4 (11%)	6 (17%)	3 (9%)
Active Doses	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
(75-125 mg)	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	44	43	43	42	42	42	35	35	35
Open-label	PI	0 (0)	1 (6%)	2 (11%)	1 (5%)	0 (0)	0 (0)	1 (6%)	0 (0)	0 (0)
Stage 2	SI	0 (0)	1 (6%)	1 (5%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Active Dose	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
(100-125 mg)	N	19	18	19	19	17	19	18	17	17

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

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

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

In a PTSD sample with prevalent lifetime history of suicidal ideation, subjects randomized to either dose group reported pre-drug suicidal ideation in blinded experimental sessions. More active dose subjects reported pre-drug positive ideation, likely due to oversampling. During blinded session 1, numbers of comparator and active dose subjects reporting positive ideation were equivalent, with only active dose subjects reporting positive ideation the next day and none serious. As active dose subjects went deeper in the therapeutic process, reports of positive ideation 6 hours post-drug increased to 17% in the blinded session 2, with no reports from comparator subjects. No subjects reported positive suicidal behavior 6 hours post-drug as they were under continuous clinical observation during treatment and for 24 hours after. 5% of active dose subjects and 8% of comparator dose subjects experienced positive ideation the next day, with none serious. Active dose session 3 was similar to the second. Interestingly, open-label experimental sessions had fewer reports of positive and serious ideation, suggesting a protective effect of receiving comparator dose sessions prior to active dose, which could be attributed to developing the therapeutic alliance.

Table 15: C-SSRS Positive and Serious Responses During Experimental Sessions and 1-Day Post-Drug for Studies MAA-1 and MDA-1 as of 01 October 2015

Condition		Session 1 N (%)			Session 2 N (%)			Session 3 N (%)		
		Pre-drug [A]	During-drug [B]	Integration Day 1	Pre-drug [A]	During-drug [B]	Integration Day 1	Pre-drug [A]	During-drug [B]	Integration Day 1
Social Anxiety in Autistic Adults										
Blinded	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	---	---	---
Placebo	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
(0 mg)	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
	N	2	2	2	2	2	2			
Blinded	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	---	---	---
Active Doses	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
(75-125 mg)	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
	N	3	3	3	3	3	3			
Open-label	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	---	---	---
Stage 2	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
Active Dose	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
(100-125 mg)	N	2	2	2	2	2	1			
Anxiety Associated with a Life-threatening Illness										
Blinded	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	---	---	---
Placebo	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
(0 mg)	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
	N	2	2	2	1	1	1			
Blinded	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Active Dose	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
(125 mg)	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	2	2	2	1	2	2	1	1	1

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

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

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

Despite prevalent lifetime history of suicidal ideation with 50% of subjects reporting serious ideation, five autistic subjects in MAA-1 reported no suicidal ideation or behavior before, during, or after experimental sessions regardless of MDMA dose. Although prevalence was about half of the PTSD and autistic subject samples, subjects with anxiety associated with a life-threatening illness also did not report suicidal ideation or behavior before, during, or after experimental sessions. These results may vary as more subjects are treated, but appear encouraging.

Table 16: C-SSRS Positive Responses During Telephone Contact Following Experimental Sessions for Studies MP-4, MP-8, MP-9, MP-12, MAA-1, and MDA-1 as of 01 October 2015

Condition		Session 1 N (%)		Session 2 N (%)		Session 3 N (%)	
		Day 2	Day 7	Day 2	Day 7	Day 2	Day 7
PTSD							
Blinded Placebo (0 mg)	PI	0 (0)	0 (0)	0 (0)	0 (0)	---	---
	SI	0 (0)	0 (0)	0 (0)	0 (0)		
	PB	0 (0)	0 (0)	0 (0)	0 (0)		
	N	4	4	4	4		
Blinded Comparator Doses (25-40 mg)	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	14	14	12	12	2	2
Blinded Active Doses (75-125 mg)	PI	5 (12%)	6 (15%)	8 (20%)	6 (15%)	4 (12%)	4 (12%)
	SI	0 (0)	0 (0)	0 (0)	1 (3%)	0 (0)	1 (3%)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	42	41	42	39	34	33
Open-label Stage 2 Active Doses (100-125 mg)	PI	3 (16%)	0 (0)	1 (5%)	0 (0)	0 (0)	0 (0)
	SI	2 (11%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	19	18	19	19	17	18
Social Anxiety in Autistic Adults							
Blinded Placebo (0 mg)	PI	0 (0)	0 (0)	0 (0)	0 (0)	---	---
	SI	0 (0)	0 (0)	0 (0)	0 (0)		
	PB	0 (0)	0 (0)	0 (0)	0 (0)		
	N	2	2	2	2		
Blinded Active Doses (75-125 mg)	PI	0 (0)	0 (0)	0 (0)	0 (0)	---	---
	SI	0 (0)	0 (0)	0 (0)	0 (0)		
	PB	0 (0)	0 (0)	0 (0)	0 (0)		
	N	3	3	3	3		
Open-label Stage 2 Active Dose (100-125 mg)	PI	0 (0)	0 (0)	0 (0)	0 (0)	---	---
	SI	0 (0)	0 (0)	0 (0)	0 (0)		
	PB	0 (0)	0 (0)	0 (0)	0 (0)		
	N	2	2	2	2		
Anxiety Associated with a Life-threatening Illness							
Blinded Placebo (0 mg)	PI	0 (0)	0 (0)	0 (0)	0 (0)	---	---
	SI	0 (0)	0 (0)	0 (0)	0 (0)		
	PB	0 (0)	0 (0)	0 (0)	0 (0)		
	N	2	2	1	1		
Blinded Active Dose (125 mg)	PI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	SI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	N	2	2	2	2	1	1

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

Reports of positive ideation during treatment continued during the week after experimental sessions in 12% to 20% of subjects randomized to active dose MDMA. Lack of reports in comparator dose subjects suggests a dose-dependent effect. Prevalence increased after the second experimental session as seen during experimental sessions, likely due to enhancement of the therapeutic process with each exposure bringing up disturbing traumatic thoughts. As MDMA is only administered in the context of psychotherapy, and PTSD subjects have a lifetime history of suicidal ideation, these effects are expected. In contrast, autistic adults and those with anxiety associated with a life-threatening illness reported no suicidal ideation or behavior.

Table 17: C-SSRS Positive Responses at Endpoints After Treatment for Studies MP-4, MP-8, MP-9, MP-12, MAA-1, and MDA-1 as of 01 October 2015

Condition		Primary/ Secondary Endpoint N (%)	End of Stage 1/ End of Stage 2 N (%)	Long-term Follow-up N (%)
PTSD				
Blinded Placebo (0 mg)	PI	0 (0)	---	---
	SI	0 (0)		
	PB	0 (0)		
	N	2		
Blinded Comparator Doses (25-40 mg)	PI	1 (8%)	0 (0)	1 (14%)
	SI	0 (0)	0 (0)	0 (0)
	PB	0 (0)	0 (0)	0 (0)
	N	12	2	7
Blinded Active Doses (75-125 mg)	PI	13 (36%)	7 (23%)	5 (31%)
	SI	1 (3%)	0 (0)	1 (6%)
	PB	0 (0)	0 (0)	0 (0)
	N	36	30	16
Open-label Stage 2 Active Doses (100-125 mg)	PI	0 (0)	1 (8%)	---
	SI	0 (0)	0 (0)	
	PB	0 (0)	0 (0)	
	N	7	13	
Social Anxiety in Autistic Adults				
Blinded Placebo (0 mg)	PI	---	0 (0)	0 (0)
	SI		0 (0)	0 (0)
	PB		0 (0)	0 (0)
	N		2	2
Blinded Active Doses (75-125 mg)	PI	---	1 (17%)	0 (0)
	SI		0 (0)	0 (0)
	PB		0 (0)	0 (0)
	N		6	3
Anxiety Associated with a Life-threatening Illness				
Blinded Placebo (0 mg)	PI	0 (0)	---	---
	SI	0 (0)		
	PB	0 (0)		
	N	1		
Blinded Active Dose (125 mg)	PI	0 (0)	0 (0)	---
	SI	0 (0)	0 (0)	
	PB	0 (0)	0 (0)	
	N	1	1	

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

About a third of active dose PTSD subjects and one comparator dose PTSD subject continued to experience suicidal ideation at the primary endpoint 1 month after treatment, but this was only serious in one case. The prevalence of suicidal ideation remained consistent at long-term follow-up, and was comparable to the pre-drug preparatory period after medication washout. Only one

autistic subject reported positive ideation during the study as a result of ending the therapeutic relationship to date.

Only five cases of suicidal ideation have been considered clinically significant across sponsor-supported studies in 122 people. Two AEs were rated serious and were not related to study drug. One SAE was reported 12 days after treatment with 30 mg MDMA and lasted 6 days, concurrent with a major depressive episode that was triggered by external trauma cues, and was treated with prescription medication and hospitalization. The other SAE was reported 9 months after treatment during the long-term follow-up period, lasted 3 days and resulted in hospitalization. Three AEs of suicidal ideation were reported during the treatment period (2 in MP-12, 1 in MAA-1), one moderate AE started on the day of an active dose experimental session and lasted 1 week, one mild AE started 1 month after the last active dose experimental session and lasted 2 days, one moderate AE started 27 days after active dose treatment, lasted 12 days and resolved after treatment with prescription medication and therapy. All cases resolved without development of suicidal behavior.

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

The Beck Depression Inventory-II (BDI-II) is a widely used self-administered measure of depression and includes an item on suicidal ideation. Subjects' depression levels were evaluated at baseline and at endpoints throughout the study, as a secondary measure of effectiveness of treatment. Tables 18 through 20 below show mean BDI-II scores for subjects in MP-4, MP-8, MP-9, MP-12, and MAA-1. Scores of 13 or lower indicate minimal, 14 to 19 mild, 20 to 28 moderate, 29 and above indicate severe depression symptoms.

Table 18: Mean BDI-II Scores at Baseline, Primary Endpoint, and End of Stage 1 by Dose for Studies MP-4, MP-8, MP-9, and MP-12 as of 01 October 2015

Condition	Baseline	Primary Endpoint	End of Stage 1
0 mg	32.5 (6.4) N=2	28.5 (9.2) N=2	---
25 mg	17.0 (0.0) N=2	15.5 (5.0) N=2	---
30 mg	30.4 (13.7) N=7	25.8 (12.2) N=6	20.0 (15.9) N=3
40 mg	23.8 (6.2) N=6	12.8 (6.9) N=5	---
75 mg	24.7 (12.6) N=7	10.3 (6.7) N=6	7.0 (5.7) N=2
100 mg	29.3 (14.2) N=8	21.9 (16.7) N=7	12.7 (9.1) N=7
125 mg	32.2 (11.0) N=30	15.8 (13.5) N=30	10.4 (12.0) N=19

As depression is not the primary indication in sponsor-supported studies, only a subset of subjects presented with clinically significant co-morbid depression at baseline, which contributes to variation within each dose group. Statistical tests have yet to be conducted, but scores appear to be trending downward in most active MDMA dose groups, indicating an improvement in depression symptoms on average.

Table 19: Mean BDI-II Scores at Secondary Endpoint, End of Stage 2, and 12-month Follow-up for Studies MP-4, MP-8, MP-9, and MP-12 as of 01 October 2015

Condition Stage 1/Stage 2	Secondary Endpoint	End of Stage 2	12-month Follow-up
0 mg/125 mg	---	---	---
30 mg/125 mg	16.5 (11.1) N=6	19.5 (13.0) N=6	17.2 (13.9) N=5
40 mg/125 mg	6.8 (6.2) N=5	9.6 (9.0) N=5	0.5 (0.7) N=2
75 mg/125 mg	9.8 (11.4) N=6	6.0 (6.3) N=5	11.2 (10.1) N=5
125 mg	---	---	12.3 (11.5) N=13

Stage 2 crossover data after initial treatment with placebo or comparator shows that depression scores are in the minimal to mild range on average after active dose treatment. Most subjects receive active dose treatments in either Stage 1 or Stage 2 and continue to long-term follow-up in PTSD studies. Depression scores remain in the minimal to mild range at 12-month follow-up, suggesting that improvements in depression observed during treatment are durable on average.

Table 20: Mean BDI-II Scores After MDMA or Placebo in MAA-1 as of 01 October 2015

Condition	Baseline Mean (SD)	1 Day Post Session 1 Mean (SD)	2 Weeks Post Session 1 Mean (SD)	1 Month Post Session 1 Mean (SD)
Placebo	3.0 (1.4) N=2	1.5 (2.1) N=2	0.0 (0.0) N=2	0.0 (0.0) N=2
MDMA (75-125 mg)	25.0 (18.1) N=3	4.7 (3.5) N=3	6.7 (9.8) N=3	11.7 (17.6) N=3
Condition		**1 Day Post Session 2 Mean (SD)**	**2 Weeks Post Session 2 Mean (SD)**	**1 Month Post Session 2 Mean (SD)**
Placebo		0.0 (0.0) N=2	0.0 (0.0) N=2	0.0 (0.0) N=2
MDMA (75-125 mg)		7.0 (3.5) N=3	5.0 (6.3) N=3	2.0 (2.8) N=2

MDMA does not worsen symptoms of depression in people exhibiting moderate to severe co-morbid depression, and may have an acute antidepressant effect in this sub-group. In most cases, symptom scores declined or remained at similar levels after MDMA-assisted psychotherapy. Some subjects experienced transient positive suicidal ideation during treatment, with these scores declining throughout the course of psychotherapy, as discussed in Section 5.3.8.5 Suicidal Ideation, Behavior, and Depression above. Taken together with C-SSRS findings that do not suggest a general increase in suicidality, improvements in depression scores indicate that MDMA-assisted psychotherapy does not exacerbate or provoke symptoms of suicidality or depression.

5.3.9 Adverse Events

5.3.9.1 Commonly Reported Adverse Events

Common AEs of MDMA reported in non-sponsor supported Phase 1 studies in healthy volunteers include elevation in blood pressure and heart rate, increased anxiety or dysphoria, and dilated pupils [8-10, 12]. Some reports indicated decreased rather than increased alertness [8]. Other common AEs reported in controlled studies of MDMA include reduced appetite, dizziness, tight jaw, bruxism (tooth-grinding), disturbance in attention, impaired gait or balance, dry mouth, and thirst. Subjects in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or recall [13], and unusual thoughts or ideas [12]. Other less commonly reported events include parasthesia (unusual body sensations) such as tingling, or feeling hot or cold. MDMA can produce anxiety in healthy volunteers [10, 12, 13]. These effects are transient and recede as drug effects wane. One study found that women were more likely than men to experience the most commonly reported adverse effects of MDMA, though men were more likely than women to experience the specific AEs of nausea and sweating [10]. Kirkpatrick and colleagues examined a pooled sample of 220 healthy volunteers from three laboratories and failed to find gender differences in subjective or cardiovascular effects [589].

The most commonly reported AEs from Phase 1 studies published between 1986 and 2012 were used to develop a list of common reactions, or Spontaneously Reported Reactions, to record daily occurrence, duration and severity [12, 13, 28, 44, 62, 205, 208, 527, 556, 559, 560, 563]. Based on the reports summarized in Table 18, 24 reactions were identified to be tracked during sponsor-supported studies MP-1 and MP-2, and three were added after examining data from the first sponsor-supported study in a PTSD sample (MP-1). The investigators noted that subjects in MP-1 reported greater incidence of Diarrhea and Muscle Tightness, which were added to the list, and further observation led to the addition of Judgment Impaired. The following 27 reactions listed by preferred terms were tracked in MP-4, MP-8, MP-9, MP-12, MAA-1, MDA-1, and MT-1: decreased appetite, diarrhea, dry mouth, judgment impaired, muscle tightness (jaw), muscle tightness, disturbance in attention, thirst, restlessness, disturbed gait, depressed mood, dizziness, hyperhidrosis, feeling cold, obsessive ruminations, sensation of heaviness, somnolence, nystagmus, parasthesia, nausea, anxiety, irritability, insomnia, asthenia, fatigue, hypersomnia, and headache.

Table 21: Mean Percentage of Subjects Reporting Commonly Reported Reactions During MDMA or Placebo Treatment Collected from 12 Phase 1 Studies Conducted Outside of Sponsor Support

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

In sponsor-supported Phase 2 studies, researchers record any spontaneous (unsolicited) report of common reactions on the day of each experimental session and 7 days after. The same severity coding system for AEs was employed throughout all studies, based on limitation in daily function. Table 19 and Table 20 above display data from 342 experimental sessions, with each subject receiving between one and six experimental sessions at different doses across Stage 1 and Stage 2. More subjects received the 100 mg to 125 mg initial dose due to additional open-label experimental sessions offered to subjects randomized to comparator and medium dose in blinded experimental sessions.

Table 22: Percentage of Observations of Most Commonly Reported Spontaneously Reported Reactions During Experimental Sessions in Studies MP-1, MP-2, MP-4, MP-8, MP-9, MP-12, MDA-1, MAA-1, and MP1-E2 as of 01 October 2015

Dose Subjects	Placebo (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Schedule	1-2 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-2 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-2 doses 3-5 weeks apart
Sessions	24	19	15	11	14	255	4
Muscle Tightness (jaw)							
Mild	2 (8%)	1 (5%)	---	1 (9%)	4 (29%)	62 (24%)	---
Moderate	3 (13%)	---	---	2 (18%)	1 (7%)	73 (29%)	1 (25%)
Severe	---	---	---	---	---	6 (2%)	1 (25%)
Total	5 (21%)	1 (5%)	0 (0%)	3 (27%)	5 (36%)	141 (55%)	2 (50%)
Anxiety							
Mild	1 (4%)	---	---	2 (18%)	4 (29%)	48 (19%)	1 (25%)
Moderate	9 (38%)	---	7 (47%)	2 (18%)	1 (7%)	61 (24%)	---
Severe	4 (17%)	---	1 (7%)	---	1 (7%)	13 (5%)	---
Total	14 (58%)	0 (0%)	8 (53%)	4 (36%)	6 (43%)	122 (48%)	1 (25%)
Decreased Appetite							
Mild	1 (4%)	2 (11%)	3 (20%)	---	4 (29%)	63 (25%)	---
Moderate	1 (4%)	1 (5%)	---	---	---	40 (16%)	1 (25%)
Severe	---	1 (5%)	---	---	---	3 (1%)	---
Total	2 (8%)	4 (21%)	3 (20%)	0 (0%)	4 (29%)	106 (42%)	1 (25%)
Headache							
Mild	5 (21%)	1 (5%)	6 (40%)	3 (27%)	10 (71%)	57 (22%)	1 (25%)
Moderate	7 (29%)	---	1 (7%)	1 (9%)	---	37 (15%)	---
Severe	---	---	---	---	---	1 (<1%)	---
Total	12 (50%)	1 (5%)	7 (47%)	4 (36%)	10 (71%)	95 (37%)	1 (25%)
Fatigue							
Mild	3 (13%)	4 (21%)	6 (40%)	---	2 (14%)	32 (13%)	---
Moderate	7 (29%)	---	2 (13%)	3 (27%)	2 (14%)	52 (20%)	---
Severe	---	---	---	---	---	3 (1%)	---
Total	10 (42%)	4 (21%)	8 (53%)	3 (27%)	4 (28%)	87 (34%)	0 (0%)
Muscle Tightness							
Mild	1 (4%)	---	5 (33%)	1 (9%)	1 (7%)	44 (17%)	---
Moderate	2 (8%)	---	2 (13%)	2 (18%)	2 (14%)	25 (10%)	---
Severe	---	---	---	---	---	---	---
Total	3 (13%)	0 (0%)	7 (47%)	3 (27%)	3 (21%)	69 (27%)	0 (0%)
Nausea							
Mild	2 (8%)	2 (11%)	1 (7%)	---	2 (14%)	34 (13%)	1 (25%)
Moderate	1 (4%)	---	2 (13%)	---	---	28 (11%)	---
Severe	---	---	---	---	---	6 (2%)	---
Total	3 (13%)	2 (11%)	3 (20%)	0 (0%)	2 (14%)	68 (27%)	1 (25%)
Feeling Cold							
Mild	2 (8%)	1 (5%)	7 (47%)	---	4 (29%)	47 (18%)	---
Moderate	1 (4%)	---	1 (7%)	---	2 (14%)	20 (8%)	---
Severe	---	---	---	---	---	1 (<1%)	---
Total	3 (13%)	1 (5%)	8 (53%)	0 (0%)	6 (43%)	68 (27%)	0 (0%)

Source: Table 31

The sponsor has analyzed the cumulative frequency of AEs commonly reported during each experimental session, collected as Spontaneously Reported Reactions. Most spontaneously reported reactions were rated as mild in studies across populations. The most frequently reported

acute and sub-acute reactions related to 255 experimental sessions with 100 mg to 125 mg initial dose of MDMA in 100 people across Phase 2 studies were muscle tightness (jaw) (141 reports during 55% of sessions at any severity, 2% severe), anxiety (122 reports during 48% of sessions at any severity, 5% severe), decreased appetite (106 reports during 42% of sessions at any severity, 1% severe), headache (95 reports during 37% of sessions at any severity, <1% severe), fatigue (87 reports during 34% of sessions at any severity, 1% severe), muscle tightness (69 reports during 27% of sessions at any severity, none severe), and nausea (68 reports during 27% of sessions at any severity, 2% severe). The next most common reactions reported during 9% to 25% of experimental sessions with a 100 mg to 125 mg initial dose of MDMA in order of frequency are: hyperhidrosis, restlessness, dizziness, insomnia, thirst, disturbed gait, dry mouth, disturbance in attention, depressed mood, and nystagmus, described in Table 31. The highest initial dose of 150 mg MDMA was only administered during four experimental sessions in MP-2, and was associated with reports of insomnia (3), muscle tightness (jaw) (2), dizziness (2), disturbed gait (2), dry mouth (2), and thirst (2), but it should be noted that this group is small. The following reactions were reported during less than 9% of experimental sessions with 100 mg to 125 mg initial dose of MDMA on the day of drug administration: feeling cold, obsessive ruminations, sensation of heaviness, somnolence, parasthesia, diarrhea, judgment impaired, irritability, asthenia, and hypersomnia. These reactions may be of less concern than previously proposed in the scientific literature on MDMA.

In studies where a low dose of MDMA (25 mg to 40 mg) was administered in 20 subjects across 45 sessions, infrequent reports of fatigue (15), anxiety (12), headache (12), muscle tightness (10), and feeling cold (9) were observed. In comparison, 12 subjects who received an inactive placebo in 24 experimental sessions reported anxiety (14), insomnia (12), headache (12), fatigue (10), and muscle tightness (jaw) (5) during experimental sessions. Taking into consideration that the 100 mg to 125 mg MDMA dose has been administered by far the most frequently, the sponsor concludes that the frequency of spontaneously reported reactions are likely to be most accurate in the 100 mg to 125 mg dose experimental sessions that have been administered to date in these studies. The higher number of experimental sessions at this dose meant that there was greater opportunity to report reactions. While 100 mg to 125 mg MDMA was associated with more reactions overall, these reactions were self-limiting and generally did not persist beyond the 7-day window after experimental sessions, unless associated with medical history.

Table 23: Percentage of Observations of Most Commonly Reported Spontaneously Reported Reactions During Telephone Contact on Day 1-7 After Experimental Sessions in Studies MP-1, MP-2, MP-4, MP-8, MP-9, MP-12, MDA-1, MAA-1, and MP1-E2 as of 01 October 2015

Dose Subjects	Placebo (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Schedule	1-2 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-2 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-2 doses 3-5 weeks apart
Observations	168	133	105	77	98	1785	21
Anxiety							
Mild	26 (15%)	4 (3%)	25 (24%)	8 (10%)	5 (5%)	239 (13%)	---
Moderate	35 (21%)	---	10 (10%)	3 (4%)	1 (1%)	172 (10%)	---
Severe	2 (1%)	---	---	---	---	24 (1%)	---
Total	63 (38%)	4 (3%)	35 (33%)	11 (14%)	6 (6%)	435 (24%)	0 (0%)
Fatigue							
Mild	23 (14%)	16 (12%)	20 (19%)	3 (4%)	27 (28%)	245 (14%)	2 (10%)
Moderate	27 (16%)	8 (6%)	8 (8%)	4 (5%)	1 (1%)	163 (9%)	14 (67%)
Severe	1 (1%)	1 (1%)	---	---	---	13 (1%)	2 (10%)
Total	51 (30%)	25 (19%)	28 (27%)	7 (9%)	28 (29%)	421 (24%)	18 (86%)
Insomnia							
Mild	19 (11%)	17 (13%)	8 (8%)	5 (6%)	6 (6%)	158 (9%)	---
Moderate	29 (17%)	13 (10%)	9 (9%)	5 (6%)	2 (2%)	88 (5%)	---
Severe	1 (1%)	8 (6%)	1 (1%)	5 (6%)	---	8 (<1%)	---
Total	49 (29%)	38 (29%)	18 (17%)	15 (19%)	8 (8%)	254 (14%)	0 (0%)
Depressed Mood							
Mild	13 (8%)	14 (11%)	4 (4%)	3 (4%)	---	114 (6%)	3 (14%)
Moderate	8 (5%)	11 (8%)	4 (4%)	---	---	101 (6%)	---
Severe	---	---	---	---	---	17 (1%)	---
Total	21 (13%)	25 (19%)	8 (8%)	3 (4%)	0 (0%)	232 (13%)	3 (14%)
Hypersomnia							
Mild	15 (9%)	8 (6%)	9 (9%)	3 (4%)	17 (17%)	145 (8%)	2 (10%)
Moderate	9 (5%)	7 (5%)	1 (1%)	3 (4%)	---	63 (4%)	---
Severe	---	---	1 (1%)	---	---	---	---
Total	24 (14%)	15 (11%)	11 (10%)	6 (8%)	17 (17%)	208 (12%)	2 (10%)
Disturbance in Attention							
Mild	11 (7%)	---	2 (2%)	2 (3%)	---	141 (8%)	---
Moderate	11 (7%)	---	2 (2%)	2 (3%)	---	38 (2%)	---
Severe	---	---	---	---	---	3 (<1%)	---
Total	22 (13%)	0 (0%)	4 (4%)	4 (5%)	0 (0%)	182 (10%)	0 (0%)
Decreased Appetite							
Mild	---	10 (8%)	2 (2%)	1 (1%)	2 (2%)	89 (5%)	---
Moderate	---	2 (2%)	---	1 (1%)	---	67 (4%)	---
Severe	---	3 (2%)	---	---	---	1 (<1%)	---
Total	0 (0%)	15 (11%)	2 (2%)	2 (3%)	2 (2%)	157 (9%)	0 (0%)
Dizziness							
Mild	5 (3%)	6 (5%)	---	---	1 (1%)	122 (7%)	---
Moderate	---	1 (1%)	---	---	---	19 (1%)	---
Severe	---	---	---	---	---	2 (<1%)	---
Total	5 (3%)	7 (5%)	0 (0%)	0 (0%)	1 (1%)	143 (8%)	0 (0%)

Dose Subjects	Placebo (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Schedule	1-2 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-2 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-3 doses 3-5 weeks apart	1-2 doses 3-5 weeks apart
Observations	168	133	105	77	98	1785	21
Irritability							
Mild	12 (7%)	3 (2%)	5 (5%)	---	4 (4%)	69 (4%)	---
Moderate	9 (5%)	---	3 (3%)	3 (4%)	---	48 (3%)	---
Severe	---	---	---	---	---	2 (<1%)	---
Total	21 (13%)	3 (2%)	8 (8%)	3 (4%)	4 (4%)	119 (7%)	0 (0%)
Headache							
Mild	9 (5%)	13 (10%)	1 (1%)	3 (4%)	4 (4%)	76 (4%)	---
Moderate	5 (3%)	13 (10%)	---	3 (4%)	---	33 (2%)	---
Severe	---	---	---	---	---	3 (<1%)	---
Total	14 (8%)	26 (20%)	1 (1%)	6 (8%)	4 (4%)	112 (6%)	0 (0%)
Muscle Tightness (jaw)							
Mild	2 (1%)	---	---	6 (8%)	2 (2%)	90 (5%)	---
Moderate	1 (1%)	---	---	4 (5%)	---	20 (1%)	---
Severe	---	---	---	---	---	2 (<1%)	---
Total	3 (2%)	0 (0%)	0 (0%)	10 (13%)	2 (2%)	112 (6%)	0 (0%)

Source: Table 32

The sponsor has analyzed the cumulative frequency of Spontaneously Reported Reactions reported during 7 days following each experimental session. The most frequently reported reactions related to 255 experimental sessions with 100 mg to 125 mg initial dose of MDMA in 100 people across Phase 2 studies were anxiety (24% of observations, 1% severe), fatigue (24% of observations, 1% severe), insomnia (14% of observations, <1% severe), depressed mood (13% of observations, 1% severe), hypersomnia (12% of observations, none severe), disturbance in attention (10% of observations, <1% severe), decreased appetite (9% of observations, <1% severe), dizziness (8% of observations, <1% severe), irritability (7% of observations, <1% severe), headache (6% of observations, <1% severe), muscle tightness (jaw and elsewhere) (6% of observations, <1% severe). The next most common reactions reported during the week after experimental sessions with 100 mg to 125 mg initial dose of MDMA in less than 6% of daily telephone contacts, in order of frequency, are: muscle tightness, nausea, obsessive ruminations, restlessness, asthenia, feeling cold, diarrhea, dry mouth, judgment impaired, disturbed gait, hyperhidrosis, sensation of heaviness, somnolence, nystagmus, parasthesia, and thirst, as described in Table 32. The highest initial dose of 150 mg MDMA was only administered during four experimental sessions in MP-2, and was associated with reports of fatigue (86% of observations), depressed mood (14% of observations), hypersomnia (10% of observations), and dry mouth (5% of observations) during the week following experimental sessions.

In studies where a low dose of 25 mg to 40 mg initial dose of MDMA was administered, infrequent reports of insomnia (22% of observations), fatigue (19% of observations), anxiety (16% of observations), depressed mood (11% of observations), headache (10% of observations), hypersomnia (10% of observations), muscle tightness (6% of observations), nausea (6% of observations), and decreased appetite (6% of observations). The following reactions were observed in 4% or less of daily telephone contact observations, in order of frequency: obsessive ruminations, irritability, muscle tightness (jaw), disturbance in attention, restlessness, dizziness, feeling cold, diarrhea, somnolence, judgment impaired, asthenia, thirst, dry mouth, hyperhidrosis, and sensation of heaviness. In comparison, 12 subjects who received an inactive placebo in 24 experimental sessions reported anxiety (38% of observations), fatigue (30% of observations),

insomnia (29% of observations), hypersomnia (14% of observations), depressed mood (13% of observations), disturbance in attention (13% of observations), and irritability (13% of observations) were reported during daily contact for 1 week following each experimental session. Headache, nausea, muscle tightness, somnolence, obsessive rumination, dizziness, muscle tightness (jaw), diarrhea, disturbed gait, and hyperhidrosis were reported in less than 10% of observations during daily telephone contact. While 100 mg to 125 mg MDMA was associated with more reactions overall, these reactions were self-limiting and generally did not persist beyond the 7-day window after experimental sessions.

Any reactions that continued beyond the 7-day window were tracked as unexpected AEs until they returned to baseline levels. In all studies to date, 18 severe reactions lasted beyond the 7-day window: insomnia (2 lasting up to 26 days), anxiety (6 lasting up to 53 days), restlessness (2 lasting up to 18 days), obsessive rumination (1 lasting 4 days) and depressed mood (4 lasting up to 51 days), headache (1 lasting 13 days), muscle tightness (jaw) (1 lasting 20 days), and muscle tightness (1 lasting 20 days). These reactions were tracked as AEs until resolution and subjects experiencing them were provided with prescription medication and additional therapy. Among the subset of AEs collected as commonly reported severe reactions, severe anxiety, insomnia, fatigue, nausea, muscle tightness, and depressed mood were reported in 4% or more subjects. Severe anxiety was reported the most during both inactive placebo (22%) and MDMA experimental sessions (5% to 10%, depending on dose). These reactions also overlap with symptoms of pre-existing conditions in medical history associated with PTSD (depression, somatic symptoms, insomnia, anxiety) and anxiety disorders, which can be exacerbated by processing traumatic content and may influence the frequency and duration of reactions observed in sponsored-supported clinical trials of MDMA-assisted psychotherapy.

5.3.9.2 Adverse Events

The sponsor has analyzed cumulative frequency of AEs through the data cut-off period, which included 122 subjects treated with MDMA at any dose in 10 MAPS-sponsored studies conducted under U.S. IND. See Table 24 below for distribution by severity and relationship. There have been no Safety Reports to date under this IND.

Table 24: Overview of All Adverse Events Post-Drug by Severity and Relationship in MAPS-Sponsored Studies Across Populations as of 01 October 2015

	Related AEs (% by severity)	All AEs (% by severity)
Mild AEs	58 (34%)	117 (36%)
Moderate AEs	100 (59%)	181 (56%)
Severe AEs	12 (7%)	28 (9%)
Any Severity	170 (100%)	326 (100%)

In data collected from all studies described above, there were 170 possibly or probably related AEs out of 326 at any severity after MDMA administration. Since MDMA is administered as an adjunct to psychotherapy, judging relationship to study drug is a known challenge for this combined therapy. In the context of complex medical histories associated with the PTSD diagnosis, somatic symptoms may wax and wane independent of treatment. In addition, it is known that processing trauma during psychotherapy for PTSD, with our without concomitant pharmacological treatment, can temporarily increase symptoms as an expected aspect of the therapeutic process. This is borne out by the high incidence of spontaneously reported reactions and AEs in the placebo group. Possibly or probably related AEs were more often moderate than mild or severe. Multiple severe AEs were rarely reported by the same subject. In Table 25 below,

body systems of AEs reported by 2% or more of subjects are displayed, with distribution and frequency of severe AEs by body system.

Table 25: Body Systems of All Adverse Events Post-Drug Reported by 2% or More of Subjects in MAPS-Sponsored Studies Across Populations

Dose	Placebo (0 mg)		Comparator Dose (25-40 mg)		Active Dose (75-150 mg)		Any MDMA Dose (25-150 mg)	
Schedule	1-2 doses 3-5 weeks apart		1-3 doses 3-5 weeks apart		1-6 doses 3-5 weeks apart		1-6 doses 3-5 weeks apart	
Subjects	14		24		141		122	
Sessions	27		49		306		355	
Relationship to Drug	PR	NR	PR	NR	PR	NR	PR	NR
Cardiac Disorders	---	---	---	---	2 (1%)	1 (1%)	2 (2%)	1 (1%)
Severe					(0)	(0)	(0)	(0)
Ear and Labyrinth Disorders	---	---	1 (4%)	---	1 (1%)	1 (1%)	2 (2%)	1 (1%)
Severe			(0)		(0)	(0)	(0)	(0)
Eye Disorders	---	---	---	---	9 (6%)	1 (1%)	9 (7%)	1 (0%)
Severe					(0)	(0)	(0)	(0)
Gastrointestinal Disorders	1 (7%)	---	1 (4%)	---	17 (12%)	13 (9%)	18 (15%)	13 (11%)
Severe	(0)		(0)		1 (1%)	(0)	1 (1%)	(0)
General Disorders and Administration Site Conditions	4 (29%)	---	4 (17%)	4 (17%)	21 (15%)	10 (7%)	25 (20%)	14 (11%)
Severe	(0)		(0)	1 (4%)	(0)	(0)	(0)	1 (1%)
Infections and Infestations	1 (7%)	4 (29%)	---	5 (21%)	6 (4%)	12 (9%)	6 (5%)	17 (14%)
Severe	(0)	(0)		(0)	(0)	2 (1%)	(0)	2 (1%)
Injury, Poisoning, and Procedural Complications	---	1 (7%)	---	---	2 (1%)	7 (5%)	2 (2%)	7 (6%)
Severe		(0)			(0)	1 (1%)	(0)	1 (1%)
Metabolism and Nutrition Disorders	---	---	---	1 (4%)	2 (1%)	2 (1%)	2 (2%)	3 (2%)
Severe				(0)	(0)	(0)	(0)	(0)
Musculoskeletal and Connective Tissue Disorders	8 (57%)	2 (14%)	1 (4%)	---	20 (14%)	13 (9%)	21 (17%)	13 (11%)
Severe	1 (7%)	(0)	(0)		(0)	1 (1%)	(0)	1 (1%)
Neoplasms Benign, Malignant, and Unspecified	---	---	---	---	---	2 (1%)	---	2 (2%)
Severe						2 (1%)		2 (2%)
Nervous System Disorders	1 (7%)	3 (21%)	3 (13%)	1 (4%)	12 (9%)	9 (6%)	15 (12%)	10 (8%)
Severe	(0)	1 (7%)	2 (8%)	(0)	(0)	(0)	2 (2%)	(0)
Psychiatric Disorders	9 (64%)	2 (14%)	11 (46%)	7 (29%)	47 (33%)	44 (31%)	58 (48%)	51 (42%)
Severe	1 (7%)	(0)	2 (8%)	3 (13%)	7 (5%)	5 (4%)	9 (7%)	8 (7%)
Renal and Urinary Disorders	---	---	---	---	2 (1%)	---	2 (2%)	---
Severe					(0)		(0)	

Dose	Placebo (0 mg)		Comparator Dose (25-40 mg)		Active Dose (75-150 mg)		Any MDMA Dose (25-150 mg)	
Schedule	1-2 doses 3-5 weeks apart		1-3 doses 3-5 weeks apart		1-6 doses 3-5 weeks apart		1-6 doses 3-5 weeks apart	
Subjects	14		24		141		122	
Sessions	27		49		306		355	
Reproductive System and Breast Disorders	---	---	---	---	---	4 (3%)	---	4 (3%)
Severe						1 (1%)		1 (1%)
Respiratory, Thoracic, and Mediastinal Disorders	1 (7%)	---	2 (8%)	---	2 (1%)	9 (6%)	4 (3%)	9 (7%)
Severe	(0)		(0)		(0)	(0)	(0)	(0)
Skin and Subcutaneous Tissue Disorders	1 (7%)	1 (7%)	---	1 (4%)	4 (3%)	3 (2%)	4 (3%)	4 (3%)
Severe	(0)	(0)		(0)	(0)	(0)	(0)	(0)
Vascular Disorders	---	---	---	---	---	3 (2%)	---	3 (2%)
Severe						(0)		(0)

PR=Possibly or probably related, NR=Not related

Across all body systems, most related AEs reported at any dose of MDMA were psychiatric disorders (48% of MDMA versus 64% of placebo subjects), followed by general disorders and administration site conditions (20% of MDMA versus 29% of placebo subjects), musculoskeletal and connective tissue disorders (17% of MDMA versus 57% of placebo subjects), gastrointestinal disorders (15% of MDMA versus 7% of placebo subjects), nervous system disorders (12% of MDMA versus 7% of placebo subjects), eye disorders (7% of MDMA versus none of placebo subjects), and infections and infestations (5% of MDMA versus 7% of placebo subjects). See Table 26 below for details of related AEs under each system organ class. Based on comparison of frequencies, taking into account that sample sizes are heavily weighted towards active dose MDMA due to study design, gastrointestinal disorders, nervous system disorders, and eye disorders appear to be associated with more MDMA subjects over placebo. Based on the elimination half-life of 7 to 9 hours for active doses of MDMA, it is difficult to judge relationship of AEs reported after the 7-day safety window as they may also be related to the therapeutic process or medical history. Investigators tended to be more conservative and judged events to be related based on known pharmacodynamics of MDMA, for example with gastrointestinal disorders and the distribution of serotonin receptors in the gut [622].

A majority of the AEs were psychiatric disorders. Given study inclusion criteria requiring a pre-existing diagnosis of chronic anxiety or PTSD and the fact that subjects were receiving MDMA, a drug that is known to increase general anxiety in an average of 19% healthy volunteers across multiple Phase 1 studies, these AEs are expected. However, the frequency of psychiatric disorders in the small group of subjects who received inactive placebo was even higher than the active doses, suggesting that these AEs may, at least in part, be related to exacerbation of medical history diagnoses during the study independent of MDMA administration.

Related AEs reported in 3% or less of MDMA subjects were: respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, cardiac, ear and labyrinth, injury, poisoning and procedural complications, metabolism and nutrition disorders, renal and urinary disorders. It is noteworthy that, although there was one related, moderate, expected cardiac AE that was deemed serious because it led to overnight monitoring of increased ventricular extrsystoles, no severe cardiac, renal and urinary, or vascular disorders were reported, and they were also the least frequently reported types of AEs after any MDMA dose, in contrast to reports of cardiovascular toxicity, hyperthermia, ARF, hyponatremia, and neurotoxicity in epidemiological settings, as described in Section 4.5 Serious Reports, Mortality, and Morbidity in Animals and Epidemiological Settings and in Table 2. The difference in frequency suggests that AEs in these body systems are likely to be rare in a controlled clinical setting with proper medical screening, and that they may receive disproportionate coverage in the scientific literature on epidemiological studies due to significant impact on the body. In Table 26 below, preferred terms of AEs possibly or probably related to comparator and active doses of study drug are presented for a more detailed view.

Table 26: Related Adverse Events in Sponsor Supported Studies of MDMA-Assisted Psychotherapy Across Populations Organized by Body System as of 01 October 2015

Dose	Comparator Dose (25-40 mg)	Active Dose (75-150 mg)	Any MDMA Dose (25-150 mg)
Schedule	1-2 doses 3-5 weeks apart	1-6 doses 3-5 weeks apart	1-6 doses 3-5 weeks apart
Subjects	22	121	122
Sessions	45	306	355
Cardiac Disorders			
Palpitations	---	1 (1%)	1 (1%)
Ventricular extrasystoles	---	1 (1%)	1 (1%)
Ear and Labyrinth Disorders			
Tinnitus	1 (5%)	---	1 (1%)
Eye Disorders			
Visual impairment	---	5 (4%)	5 (4%)
Vitreous floaters	---	1 (1%)	1 (1%)
Dry eyes/abnormal sensation in eye	---	1 (1%)	1 (1%)
Vision blurred	---	2 (2%)	2 (2%)
Gastrointestinal Disorders			
Diarrhea	1 (5%)	4 (3%)	5 (4%)
Dyspepsia	---	3 (2%)	3 (2%)
Abdominal pain	---	3 (2%)	3 (2%)
Nausea	---	2 (2%)	2 (2%)
Oropharyngeal blistering	---	1 (1%)	1 (1%)
Vomiting	---	4 (3%)	4 (3%)
General Disorders and Administration Site			
Asthenia	---	1 (1%)	1 (1%)
Fatigue	4 (18%)	9 (7%)	13 (11%)
Feeling abnormal	---	1 (1%)	1 (1%)
Feeling hot	---	2 (2%)	2 (2%)
Irritability	---	1 (1%)	1 (1%)
Pain (body aching, body tension)	---	4 (3%)	4 (3%)
Pyrexia	---	1 (1%)	1 (1%)
Chills	---	1 (1%)	1 (1%)
Infections and Infestations			
Pharyngitis streptococcal	---	1 (1%)	1 (1%)
Upper respiratory infection	---	3 (2%)	3 (2%)
Urinary tract Infection	---	2 (2%)	2 (2%)
Injury, Poisoning, and Procedural Complications			
Contusion	---	1 (1%)	1 (1%)
Skin abrasion	---	1 (1%)	1 (1%)
Metabolism and Nutrition Disorders			
Anorexia	---	1 (1%)	1 (1%)
Decreased appetite	---	1 (1%)	1 (1%)

Dose	Comparator Dose (25-40 mg)	Active Dose (75-150 mg)	Any MDMA Dose (25-150 mg)
Schedule	1-2 doses 3-5 weeks apart	1-6 doses 3-5 weeks apart	1-6 doses 3-5 weeks apart
Subjects	22	121	122
Sessions	45	306	355
Musculoskeletal and Connective Tissue Disorders			
Arthralgia (joint)	---	1 (1%)	1 (1%)
Back pain	---	2 (2%)	2 (2%)
Joint stiffness	---	1 (1%)	1 (1%)
Muscle spasms	---	1 (1%)	1 (1%)
Muscle tightness	1 (5%)	7 (6%)	8 (7%)
Muscle twitches	---	1 (1%)	1 (1%)
Musculoskeletal pain (shoulder)	---	3 (2%)	3 (2%)
Myalgia	---	3 (2%)	3 (2%)
Neck pain	---	1 (1%)	1 (1%)
Nervous System Disorders			
Burning sensation (fingers, thighs)	---	2 (2%)	2 (2%)
Dizziness	---	1 (1%)	1 (1%)
Hangover (feeling hungover)	---	1 (1%)	1 (1%)
Headache	1 (5%)	3 (2%)	4 (3%)
Hypersomnia	1 (5%)	3 (2%)	4 (3%)
Hypoaesthesia facial	---	1 (1%)	1 (1%)
Migraine headache	1 (5%)	---	1 (1%)
Myoclonus	---	1 (1%)	1 (1%)
Tension headache	---	1 (1%)	1 (1%)
Psychiatric Disorders			
Agitation	---	1 (1%)	1 (1%)
Anxiety	4 (18%)	22 (18%)	26 (21%)
Bruxism	---	2 (2%)	2 (2%)
Depressed mood	3 (14%)	4 (3%)	7 (6%)
Derealization	---	1 (1%)	1 (1%)
Dissociation	---	1 (1%)	1 (1%)
Disturbance in attention	---	1 (1%)	1 (1%)
Flashback	---	1 (1%)	1 (1%)
Hypnagogic hallucination	---	1 (1%)	1 (1%)
Hypnopompic hallucination	---	1 (1%)	1 (1%)
Intentional self-injury	---	1 (1%)	1 (1%)
Irritability	---	2 (2%)	2 (2%)
Negative thoughts	1 (5%)	---	1 (1%)
Obsessive Rumination	1 (5%)	1 (1%)	1 (1%)
Panic attack	---	4 (3%)	1 (1%)
Restlessness	---	1 (1%)	1 (1%)
Suicidal ideation	---	1 (1%)	1 (1%)
Tic (teeth tapping)	---	1 (1%)	1 (1%)
Time perception altered	1 (5%)	---	1 (1%)
Trichotillomania	1 (5%)	---	1 (1%)
Renal and Urinary Disorders			
Nocturia	---	1 (1%)	1 (1%)
Dysuria	---	1 (1%)	1 (1%)

Dose	Comparator Dose (25-40 mg)	Active Dose (75-150 mg)	Any MDMA Dose (25-150 mg)
Schedule	1-2 doses 3-5 weeks apart	1-6 doses 3-5 weeks apart	1-6 doses 3-5 weeks apart
Subjects	22	121	122
Sessions	45	306	355
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	1 (5%)	---	1 (1%)
Nasal congestion	1 (5%)	2 (2%)	3 (2%)
Sinus headache	---	1 (1%)	1 (1%)
Skin and Subcutaneous Tissue Disorders			
Petechiae	---	2 (2%)	2 (2%)
Pruritis	---	2 (2%)	2 (2%)

The most frequently reported possibly or probably related AEs were anxiety (18% in active versus 18% comparator subjects), fatigue (7% active versus 18% comparator subjects), muscle tightness (6% active versus 5% comparator subjects), and visual impairment (4% active versus none of comparator subjects). Subjective effects of MDMA are known to have a dose response relationship, so AEs with equivalent frequencies across comparator versus active doses of MDMA suggest an absence of dose response and possible relationship to medical history or therapeutic process. Since more individuals received active dose MDMA due to unequal group sizes weighted towards the active MDMA doses, and the partial crossover offered to comparator dose and placebo subjects, a greater number of AEs is expected with active doses of MDMA beyond any expected dose response relationship. In addition, frequencies in comparator dose subjects are based on a small sample of 22 subjects who received 45 experimental sessions.

Muscle tightness in the body as well as specific to the jaw was frequently reported as an unsolicited reaction during experimental sessions, as described in Table 22. During the 7-day safety window, these reactions were much less frequently reported, as described in Table 23 and Table 32. Among related AEs reported during and after drug administration, somatic symptoms were more frequently experienced in active dose subjects, such as pain associated with body tension (3% of active dose subjects versus none of comparator subjects), muscle tightness (6% of active dose versus 5% of comparator dose subjects), musculoskeletal pain in the shoulder (2% of active dose subjects versus none of comparator), back pain (2% of active dose subjects versus none of comparator), and myalgia (2% of active dose subjects versus none of comparator). As previously discussed in Section 5.3.9.2 Adverse Events, it is difficult to judge relationship between study drug and conditions associated with medical history diagnoses. Pain and somatic symptoms can be directly related to traumatic events, such as physical or sexual assault, a motor vehicle accident, or combat [623]. A meta-analytic review and several large studies have found a robust association between PTSD and somatic symptoms, suggesting that PTSD itself may be a contributing factor beyond combat exposure, sexual, or physical abuse that lead to the PTSD [624-627].

Although MDMA is not a classic hallucinogen, as classified by chemical structure and mechanism of action, data from sponsor-supported studies suggest that in a clinical population mild psychoactive effects, such as hypnagogic and hypnopompic hallucinations and visual distortions may be observed in some individuals. Hallucinogenic subjective effects were not actively solicited during therapy sessions, as was done in Phase 1 studies of healthy volunteers [8, 10, 11, 556]. Any unsolicited reports were collected as spontaneously reported reactions or AEs in sponsor-supported studies.

Table 27: Severe Related Adverse Events in Sponsor Supported Studies of MDMA-Assisted Psychotherapy Across Populations as of 01 October 2015

Indication	PTSD	Healthy	Anxiety	Social Anxiety	Total
Population	All	Therapists	Life-Threatening Illness	Autistic Adults	
Subjects	107	7	4	9	127
Sessions	365	7	8	19	399
Psychiatric					
Re-experiencing Episode	1	---	---	---	1 (1%)
Panic Attack	2	---	---	---	2 (2%)
Depressed Mood	2	---	---	---	2 (2%)
Obsessive Rumination	1	---	---	---	1 (1%)
Anxiety	3	---	---	---	3 (2%)
Nervous System					
Headache	1	---	---	---	1 (1%)
Gastrointestinal					
Abdominal Cramps/Pain	1	---	---	---	1 (1%)
General					
Restlessness	1	---	---	---	1 (1%)
Musculoskeletal & Connective Tissue					
Musculoskeletal Chest Pain	1	---	---	---	1 (1%)

The sponsor has analyzed the cumulative frequency of AEs and found the most frequent severe possibly or probably related AEs to be anxiety or distress (N=3, 2% of subjects), depressed mood (N=2, 2% of subjects), and panic attacks (N=2, 2% of subjects) in sponsor-supported PTSD studies. The following severe related AEs were observed in 1% of subjects: re-experiencing episode, obsessive rumination, restlessness, headache, abdominal cramps/pain, and musculoskeletal chest pain. Severe related AEs were treated with prescription medications and followed by additional phone contact and psychotherapy to ensure that the subjects returned to baseline or were stabilized. It is noteworthy that no severe related AEs were reported in non-PTSD populations in sponsor-supported studies, which could also be attributed to small sample sizes.

5.3.9.3 Serious Adverse Events

Eleven SAEs have occurred across five sponsor-supported studies. These include one expected related SAE and 10 unrelated SAEs after drug administration. See Table 28 below for a summary of these SAEs.

Table 28: Serious Adverse Events in Sponsor-Supported Studies of MDMA-Assisted Psychotherapy Across Populations as of 01 October 2015

Dose		Comparator Dose (30 mg)	Active Dose (100 mg)	Active Dose (125 mg)
System Organ Class Preferred Term	**Relationship**			
Gastrointestinal Disorders				
Appendicitis	None			1
Injury, Poisoning, and Procedural Complications				
Fractured Clavicle (auto accident)	None			1
Lower Limb Fracture	None		1	
Nervous System Disorder				
Vasovagal Syncope	None			1
Neoplasms Benign, Malignant, and Unspecified				
Brain Metastasis (frontal brain syndrome)	None			1
Breast Cancer	None			1
Reproductive System and Breast Disorders				
Ovarian Cyst Ruptured	None		1	
Psychiatric Disorders				
Suicidal Ideation	None	1		1
Major Depressive Episode	None			1
Cardiac Disorders				
Increase in Ventricular Extrasystoles	Probably			1

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

5.3.10 Abuse Potential

When reviewing the effects of MDMA in a sample of 74 largely drug-naïve subjects in a study conducted outside of sponsor support, Liechti and colleagues stated that "none of the subjects expressed any interest in taking MDMA as a recreational drug" after receiving MDMA in a

controlled research setting [10]. When assessed in terms of willingness to choose money over receiving the drug, subjects previously experienced with Ecstasy provided similar responses to 2 mg/kg MDMA and 20 mg d-amphetamine, a sign of having reinforcing effects [596]. A study that enrolled subjects with a history of Ecstasy use (4 to 40 occasions) found that only self-reported feelings of playfulness were associated with subjects' desire to take MDMA in a controlled research setting [39].

The sponsor has assessed abuse potential of MDMA in Phase 2 clinical trials with collection of self-report information on Ecstasy use during long-term follow-up in all studies. In addition, one study (MP-2) incorporated random and scheduled drug testing during long-term follow-up. One subject in MP-1 who had received two experimental sessions with active dose MDMA reported the use of Ecstasy in an attempt to recreate the therapeutic setting but found the experience unsatisfactory, and after this experience indicated no desire to repeat it. No other subjects in this study reported using Ecstasy after completing the study [42]. In sponsor-supported study MP-2, drug screens specific for MDMA performed 2 months, 6 months, and 12 months after the final experimental session were negative, suggesting that study subjects did not seek out MDMA or Ecstasy after taking part in the study. Although MDMA does not demonstrate signals associated with known abuse liability patterns, the drug will only be administered in a clinic setting under continuous observation on an intermittent schedule, which further limits abuse potential.

5.4 Efficacy of MDMA Across Populations

5.4.1 PTSD

Ongoing and completed sponsor-supported studies of MDMA-assisted therapies employ recognized clinician-administered gold-standard measures of the condition or symptoms. The primary outcome measure of efficacy for studies of MDMA-assisted psychotherapy for PTSD to date is the Clinician Administered PTSD Scale (CAPS) following DSM-IV, an established semi-structured interview conducted by a trained clinician [628-630]. The Global Severity CAPS score encompasses frequency and intensity scores for three symptom domains; re-experiencing, avoidance and hyperarousal. An independent rater that does not see the subjects during any of the psychotherapy sessions administers the CAPS at baseline and at the primary endpoint, 1 or 2 months after blinded MDMA-assisted psychotherapy sessions. Secondary endpoints include an assessment 1 to 2 months after a third experimental session and 12 months after the last treatment.

Analyses of the CAPS at the primary endpoint after two experimental sessions in MP-1 found subjects receiving MDMA-assisted psychotherapy experienced a clinically and statistically significant decline in PTSD symptoms compared to placebo-assisted psychotherapy [41]. Global CAPS scores declined for all subjects over time (overall baseline mean Global CAPS=79.1±21.7, and 2 months after the second experimental session, mean Global CAPS=38.2±30.3), indicating a clinically significant drop of 40.9 points, and a 52% reduction in symptoms. People in the MDMA and placebo conditions began the study with similar CAPS scores, while CAPS scores after experimental sessions were lower for people in the MDMA condition through 2 months after the second experimental session (Placebo=59.1±28.9 versus MDMA, 25.4±23.95). Placebo subject scores dropped 20.5 points 2 months after the second experimental session while MDMA subject CAPS scores dropped 53.3 points, or a 26% drop in PTSD symptoms for controls versus a 68% drop in PTSD symptoms for MDMA subjects.

The second study of MDMA-assisted psychotherapy (MP-2) found results similar to the MP-1 study, but improvement after three blinded experimental sessions with 125 mg MDMA was numerically but not statistically superior to the 25 mg MDMA comparator dose [43]. CAPS

scores declined over time for the eight subjects given 125 mg MDMA (baseline mean=66.4±13.6 versus 3 weeks after the third experimental session mean=50.7±19.7), indicating a drop of 15.7 points, or a 23.5% decrease in scores. On the other hand, CAPS scores increased slightly over time for the four subjects given comparator dose (baseline mean=63.2±7.9 versus 3 weeks after the third experimental session mean=66.5±7.5), indicating an increase of 2.3 points, or a 5.2% increase in CAPS scores.

Table 29 and Table 30 below show pooled mean Global CAPS Scores for completed (MP-1, MP-2) and ongoing sponsor-supported studies (MP-4, MP-8, MP-9, MP-12). Since data collection is still in progress, formal analyses have yet to be executed, but data trends appear similar to published reports, with a medium to large effect size of active dose MDMA-assisted psychotherapy depending on number of experimental sessions completed. Table 29 below depicts mean Global CAPS scores for each condition at Baseline, 1 to 2 months after the second experimental session (Primary Endpoint), and 1 to 2 months after the third experimental session (End of Stage 1). Placebo and comparator groups cross over to Stage 2 after the Primary Endpoint, therefore CAPS is not administered at the End of Stage 1 for these groups. Active dose groups (100 mg and 125 mg) do not crossover, hence no data for Stage 2 endpoints. Long-term follow-up data collection is ongoing.

Table 29: Mean Global CAPS Scores in Stage 1 of Sponsor-Supported Studies of MDMA-Assisted Psychotherapy for PTSD as of 01 October 2015

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)
0 mg	83.6 (21.11) N=10	62.9 (27.04) N=10	---
25 mg	70.4 (10.01) N=8	61.2 (8.18) N=6	66.5 (7.55) N=4
30 mg	87.4 (14.12) N=7	73.5 (24.58) N=6	62.7 (36.12) N=3
40 mg	91.0 (17.89) N=7	80.6 (18.81) N=5	---
75 mg	82.4 (17.32) N=7	24.0 (18.79) N=6	18.5 (9.19) N=2
100 mg	94.4 (20.17) N=9	71.0 (30.85) N=7	40.9 (20.92) N=7
125 mg	84.13 (19.01) N=56	46.0 (31.46) N=53	42.4 (27.21) N=34

Across studies, CAPS scores are downward trending at the primary endpoint after two experimental sessions of MDMA-assisted psychotherapy. Formal pooled analyses to determine statistical significance have not been conducted as data collection is ongoing. Primary endpoint results after active doses of 75 mg to 125 mg initial dose, with an optional supplemental half-dose administered 1.5 to 2.5 hours later, appear lower than placebo or comparator dose results after two experimental sessions. Two-month follow-up results at the End of Stage 1 after a blinded or open-label third experimental session demonstrate signals of efficacy that should be further explored in a blinded three session treatment model of MDMA-assisted psychotherapy.

Table 30: Mean Global CAPS Scores in Stage 2 and Long-term Follow-up of Sponsor-Supported Studies of MDMA-Assisted Psychotherapy for PTSD as of 01 October 2015

Condition Stage 1/Stage 2	Last Stage 1 Observation Mean (SD)	Secondary Endpoint Mean (SD)	End of Stage 2 Mean (SD)	12-month Follow-up Mean (SD)
0 mg/125 mg	62.9 (27.04) N=10	33.9 (12.8) N=7	33.6 (18.6) N=5	18.7 (7.6) N=6
25 mg/125 mg	61.2 (8.18) N=6	42.5 (25.3) N=4	36.8 (13.6) N=4	31.5 (19.2) N=4
30 mg/125 mg	73.5 (24.58) N=6	46.5 (20.5) N=6	46.2 (30.5) N=6	59.0 (42.6) N=5
40 mg/125 mg	80.6 (18.81) N=5	38.6 (29.2) N=5	35.2 (31.1) N=5	14.0 (19.8) N=2
75 mg/125 mg	24.0 (18.79) N=6	22.3 (18.9) N=6	22.2 (20.5) N=5	26.8 (21.2) N=5
100 mg	40.9 (20.92) N=7	---	---	37.0 N=1
125 mg	42.4 (27.21) N=34	---	---	34.6 (28.1) N=30

Across studies, CAPS scores are also downward trending at the secondary endpoint after two open-label experimental sessions of MDMA-assisted psychotherapy and are consistent with Stage 1 results. Secondary endpoint results in the crossover set receiving an active dose of 125 mg MDMA after receiving comparator dose or placebo in Stage 1 are in range with subjects receiving 100 mg or 125 mg in Stage 1. Comparison between the 75 mg MDMA results in Stage 1 and the Stage 2 results suggest that this dose is also active and receiving additional 125 mg MDMA sessions does not lead to further improvement in this small sample. Formal analyses to determine statistical significance within-subjects have not been conducted as data collection is ongoing. Twelve-month follow-up results after all subjects have received active dose MDMA in either Stage 1 or Stage 2 suggest that the integration process may continue and lead to further improvement of PTSD symptoms in some subjects.

5.4.2 Social Anxiety in Autistic Adults

The primary outcome measure for the study of social anxiety in people on the autism spectrum is the Liebowitz Social Anxiety Scale (LSAS). This observer-blind measure is an established clinician-administered measure of social anxiety, assessing fear and avoidance in different situations. The LSAS consists of 24 items, with each item rated on a four-point scale (from 0 to 3), with subscales for performance fear, performance avoidance, social fear, and social avoidance. The study is ongoing and efficacy findings will not be presented in this version of the IB.

Data is being collected on the effects of two sessions of MDMA-assisted therapy in people on the autism spectrum with social anxiety symptoms. The study is still blinded; therefore, efficacy data is not presented.

5.4.3 Anxiety Associated with Life-Threatening Illness

MAPS is studying a new indication, the effects of MDMA-assisted psychotherapy on people experiencing anxiety as they face of a potentially life-threatening illness. No data is available at this time.

6.0 Summary of Data and Guidance for the Investigator

MDMA is a psychoactive compound that affects mood, perception, and increases prosocial feelings. The sponsor is investigating use of this compound as an adjunct to psychotherapy for treating PTSD, social anxiety in people on the autism spectrum, and anxiety related to a life-threatening illness. Researchers with and without sponsor support have conducted *in vitro* and *in vivo* non-clinical and clinical studies with MDMA, and additional clinical trials are ongoing. At this time, MDMA is listed as a Schedule I controlled substance in the U.S. and is not permitted for medical use outside of research settings. Psychotherapists in the U.S. began to use MDMA as an adjunct to psychotherapy in the mid to late 1970s, and narrative accounts describe therapeutic use prior to its scheduling. MDMA was administered to thousands of people in a therapeutic setting prior to scheduling, and has been administered to approximately 1180 people in controlled research settings as of 01 October 2015. These studies have demonstrated that MDMA can be safely administered to people with PTSD in a controlled clinical setting.

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

6.1 Pharmacology

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

The pharmacokinetics of MDMA in humans has been characterized using oral doses of up to 150 mg MDMA in humans. MDMA disposition in the body follows nonlinear pharmacokinetics. MDMA is metabolized in the liver by several enzymes. It is likely that active doses of MDMA saturate CYP2D6 function for an extended period, with function normalizing up to 10 days post-MDMA. The enzymes CYP1A2, COMT, and MAO may also be involved in the metabolism of MDMA. MDMA is metabolized by *N*-demethylation to MDA. The parent compound and MDA are further *O*-demethylenated 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. This window should be considered when evaluating relationship of AEs to MDMA.

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

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

6.2 Toxicology

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

Extensive preclinical toxicological studies report that high or repeated doses of MDMA can increase locomotor activity and signs of serotonin syndrome, which can damage serotonergic axons originating in the brainstem dorsal raphe nuclei, probably as a result of oxidative stress, and this damage is associated with decreases in serotonin production, serotonin metabolites, and SERT site densities. While these findings are consistent across studies, studies in low to moderate Ecstasy users do not report an increase in a biological marker of neuronal injury, and only one of three studies of this marker in humans detected it in heavy users. Retrospective studies in Ecstasy users have found contradictory effects on visual and verbal memory, planning and making decisions, and some types of visual processing. An uncontrolled prospective study of moderate

Ecstasy users failed to find changes in SERT sites or signs of neuronal injury; slight changes in cerebral blood flow in the dorsolateral PFC were found. In the same study, Ecstasy users showed less improvement on a memory task than non-users. Taken together, these findings suggest possible indications of cumulative toxicity in chronic high dose dosing regimens.

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

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

6.3 Physiological Effects

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

Subjects enrolled in controlled Phase 1 single dose MDMA trials conducted without sponsor support had elevations above a pre-determined cut-off of at least 140/90 mmHg (approximately 5% per trial). All subjects in a subsequent trial in a separate sample given a regimen of 50 mg followed by 100 mg 2 hours later had blood pressure elevations above 140/90 mmHg. Based on the literature, effects of the initial dose of MDMA on blood pressure and heart rate are expected to have a linear dose-response relationship, and the supplemental dose may have an effect on SBP elevation. In sponsor-supported studies, SBP above 160 mmHg was detected in 27% of experimental sessions where MDMA was administered at any dose, and in 35% of subjects in sponsor-supported trials overall. The majority of these instances occurred with the 125 mg MDMA dose group. Both peak and longest duration of blood pressure elevation were also observed in the 125 mg MDMA group. Maximum duration of SBP above 160 mmHg was 6 hours in two subjects with peak values of 172 and 174, respectively. MDMA doses of 40 mg and greater were associated with SBP above 160 mmHg, supporting a dose dependent effect of MDMA on blood pressure. DBP above 110 mmHg was observed in only 5% of experimental sessions with MDMA at any dose in 7% of subjects. The majority of these instances occurred with the 125 mg MDMA dose. Maximum duration of DBP above 110 mmHg was 5 hours. Heart rate above 110 bpm was detected in 31% experimental sessions where MDMA was administered at any dose, in 39% of subjects in sponsor-supported trials. Both peak and maximum duration above 110 bpm were observed in 125 mg MDMA sessions. The highest pulse observed was 160 bpm for 1 hour. Maximum duration above 110 bpm was 9.5 hours. A comparison of subjects receiving the supplemental dose to those who only received the initial dose in MP-1 indicate that the supplemental dose did not cause further elevation in blood pressure and heart rate beyond the initial dose.

Candidates with controlled hypertension are excluded from participation in all but one of sponsor-supported studies to limit cardiovascular risk during treatments. In MP-8, the only study that did enroll a sub-group of subjects with controlled hypertension, SBP above 160 mmHg was detected in 75% (3 of 4) of subjects and 67% (8 of 12) of experimental sessions where MDMA was administered to this sub-group. The prevalence of these elevations appears higher in this sub-group than the overall sample, although the prevalence could decrease in a larger group. Pre-drug SBP was typically higher in this sub-group, and peak SBP of these subjects was typically at the upper end of the range of the overall sample. Final SBP readings remained 11 to 14 mmHg higher than pre-drug SBP readings in one of three subjects. The single subject with extended duration of SBP elevation had a medical history of both hypertension and hyperlipidemia. The same subject had DBP above 110 mmHg in each experimental session, suggesting that pre-existing cardiovascular risk factors beyond hypertension itself may be associated with further elevations in

blood pressure, though a larger sample would be needed to establish this. None of the subjects with controlled hypertension experienced AEs of the cardiovascular system.

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

Body temperature greater than 1°C above baseline was detected in 33% of experimental sessions in which MDMA was administered at any dose, in 46% of subjects in sponsor-supported trials, with most of these cases observed in sessions with 125 mg MDMA. In contrast, in 7% of experimental sessions in which inactive placebo was administered, and in 14% of subjects receiving inactive placebo, elevation of body temperature above cut-off was observed. Both peak and longest duration of body temperature elevation were observed in the 125 mg MDMA group. Maximum peak in all sessions was 38.7°C lasting 3 hours, and maximum duration of elevation in all sessions was 9.2 hours, in separate subjects. Vital signs in sponsor-supported Phase 2 studies presented above suggest a dose-dependent action on SBP and pulse, which is consistent with the literature on healthy volunteers. Body temperature and DBP do not appear to be strongly related to MDMA dose. No subjects receiving MDMA in sponsor-supported clinical trials have required any clinical interventions for elevated vital signs, as all values returned to normal as the effects of MDMA diminish.

6.3.1 Immunological Effects

Humans exhibit transient immunological changes after a dose of 100 mg, including reduced numbers of CD4 cells, increased numbers of NK cells, and an increase in levels of immunosuppressive and anti-inflammatory cytokines compared with levels of pro-inflammatory and immunostimulating cytokines. In several respects, these effects are similar to those that occur with other psychoactive substances, so are not unique to MDMA. Immunological effects last for approximately 24 hours after administration, and most arise indirectly from serotonin release. The significance of these immunological effects remains unclear. Previous reports did not show increases in infections after MDMA and data from the study of MDMA-assisted psychotherapy has reported only instances of infection (upper respiratory or urinary tract) within 7 days of MDMA administration. Based on results from trials conducted by the sponsor, the impact of these effects is expected to be modest. The investigators may exclude subjects that might face additional risks from immunosuppression.

6.3.2 Hepatic Effects

Phase 1 studies conducted outside of sponsor support involving administration of MDMA to healthy volunteers have not published any results of liver function after MDMA administration. There have been no reported adverse effects on the liver from these studies. The first two sponsor-supported Phase 2 studies (MP-1, MP-2) assessed liver function after completion of two or three blinded experimental sessions. No clinically or statistically significant changes in liver

function occurred in MP-1. Values for laboratory tests were within the normal range in MP-1. No AEs related to liver function have been reported in subsequent sponsor-supported studies. Only two subjects in the MP-2 study reported two clinically significant hepatic abnormalities, with one likely due to hereditary factors and the other indicating inflammation in a subject with a medical history of breast cancer 3 months after the last administration of MDMA as an AE unrelated to the study drug.

6.4 Suicidal Ideation, Behavior, and Depression

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

Overall the incidence of serious suicidal ideation or behavior in sponsor-supported studies is low, occurring in only a few subjects post-MDMA treatment, and returning to non-life-threatening scores while subjects are closely monitored. Given that people suffering from severe PTSD are known to experience suicidal ideation and behavior, it is difficult to identify a single cause of the increase in suicidal thinking or behavior (i.e. exacerbation of PTSD symptoms related to medication withdrawal or to the psychotherapeutic process, or from MDMA effects). A large percentage of people enrolled in the studies reported suicidal ideation and behavior during sometime in their lives prior to study enrollment, which may reflect a manifestation of PTSD or co-morbid affective disorders. When positive serious ideation or behavior occurred after study enrollment, the investigators made follow-up observations of C-SSRS to ensure subject safety, and tracked scores until they returned to non-serious levels. Only two incidences of suicidal ideation have been considered clinically significant and tracked as severe AEs, but they were reported during the long-term follow-up period and were not related to study drug.

6.5 Adverse Events

Overall, adverse effects of MDMA are modest and generally have not been associated with serious discomfort in healthy volunteers or in people with PTSD. Risks posed by sympathomimetic effects of MDMA treatments are addressed in MAPS' clinical trials by excluding people with pre-existing cardiovascular disease, cerebrovascular disease or uncontrolled hypertension and by monitoring blood pressure, body temperature, and pulse. Common reactions reported in clinical trials are transient and diminish as drug effects wane during the MDMA session and over the next 24 hours. Once the drug leaves the body, 3 to 4 days post-treatment, most reactions diminish. Reactions are monitored daily for 1 week after each

treatment and followed until resolution. The most common acute reactions at any severity include muscle tension in the jaw, exacerbation of anxiety, decreased appetite, muscle tension, nausea, and feeling cold. Headache and fatigue are commonly reported across MDMA and placebo groups, and are likely to be background events. During the week after each experimental session, the most commonly reported reactions at any severity were anxiety, fatigue, insomnia, depressed mood, hypersomnia, difficulty concentrating, decreased appetite, and dizziness in the active dose MDMA groups across studies, with PTSD studies overrepresented. Of these reactions, only decreased appetite and dizziness were appreciably elevated above the placebo group, and the remaining reactions are likely to be background events. Severe unexpected AEs included abdominal cramps, panic attacks, and the following reactions lasting longer than 7 days: anxiety, headache, low mood, rumination, and restlessness, all reported in studies of MDMA-assisted psychotherapy for PTSD. All subjects fully recovered from these events.

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

6.6 Risk Mitigation in MDMA-Assisted Clinical Trials

Investigators must establish subject eligibility prior to enrollment in trials with MDMA, with eligibility established through medical history, physical examination, vital signs, clinical laboratory tests, EKG, psychiatric interview, and assessment of relevant psychiatric symptoms. Additional procedures may be used as indicated, such as exercise tests and carotid ultrasound imaging. If the study is investigating use of MDMA in people with a specific psychiatric condition, then the investigators must also determine whether an individual has the condition and that specified exclusion criteria are absent.

MDMA-assisted psychotherapy clinical trials use questionnaire-based measures and clinical interviews that can cause testing fatigue and/or emotional reactions stemming from discussing trauma or other psychological stressors. Investigators should be experienced in treating the condition under investigation and they should seek to minimize testing fatigue and emotional stress during screening and participation in the study. Subjects enrolled in studies of MDMA-assisted psychotherapy should be prepared to engage in processing their trauma, which requires proper facilitation and support from study therapists. MDMA-assisted psychotherapy will always be performed in controlled clinical settings to mitigate risk. It is best to ensure that the controlled setting for treatments with MDMA-assisted psychotherapy has the capacity to control ambient temperature for subject comfort, though there is no evidence that this will significantly influence or is needed for control of core body temperature. Cardiovascular risk is primarily mitigated through rigorous screening to exclude subjects with uncontrolled cardiovascular risk. During experimental sessions, therapists should monitor for clinical signs and symptoms (severe headache, confusion or focal neurologic signs, vision problems, chest pain, difficulty breathing, or palpitations) and add more frequent vitals measurements only if clinically indicated. Investigators conducting trials of MDMA should be prepared to treat elevated blood pressure with medications if needed, and either to provide appropriate care related to these effects or to transport individuals to an emergency department, if necessary.

Discontinuing pre-study medications and the acute/sub-acute effects of MDMA-assisted psychotherapy can produce shifts in mood and activation, which may transiently increase likelihood of suicidal ideation or behavior. In addition, during treatment of subjects with prevalent lifetime history of suicidal ideation, the active dose of MDMA, which catalyzes the therapeutic process, can be associated with suicidal ideation as a result of processing trauma. To mitigate risk, subjects are kept under continuous clinical observation during experimental sessions. Experimental sessions are followed by an overnight residential stay at the study site to allow the integration process to begin, followed by an integrative psychotherapy session on the following day, daily phone contact for 1 week, with channels of easy access to the treating therapists maintained during the studies. The need for additional support in these studies is continually assessed with the General Well Being and AE monitoring. Due to the psychotherapeutic setting in which MDMA is provided in these studies, exacerbations of symptoms often appear to be related to the therapeutic process rather than directly to the MDMA itself. When assessing potential AEs, investigators should consider baseline severity of conditions and symptoms, therapeutic process, and potential relationship to drug administration throughout the study.

In sponsor-supported studies, 18% of people across active dose and comparator dose groups experienced periods of increased anxiety (2% severe) and 3% experienced panic attacks, all in the active dose MDMA group (2% severe). Psychological distress may arise at any time during an MDMA-assisted psychotherapy session from the time of first drug effects until effects have dissipated approximately 3 to 5 hours after administration. Anxiety or distress during the session may last for as little as 15 minutes or for as long as 5 hours or more and may be related to the therapeutic process itself. In addition, psychological distress could arise following an MDMA session as a result of subjects having difficulty integrating their experience after the effects of MDMA have subsided. In previous Phase 1 and Phase 2 studies, these symptoms have been modest and self-limiting, and have responded well to reassurance from the investigator, with occasional use of benzodiazepines for anxiety after the experimental session. In clinical trials of PTSD treatment, subjects are informed that experimental sessions are intended to include periods of confronting and working through traumatic experiences. Hence signs of psychological distress, anxiety, or other unpleasant psychological reactions are to be expected and may be considered an element of the psychotherapeutic process. In Phase 1 trials with normal healthy volunteers, mild anxiety and depressed mood were reported by some subjects 1 to 3 days after MDMA administration. It is not known whether these reactions resulted from direct effects of MDMA, or from psychological content that may have been accessed during the MDMA experience.

The potential for destabilizing psychological distress can be minimized by:

- Exclusion of people who might be more vulnerable to psychological destabilization if tapered off other psychiatric drugs, such as people diagnosed with bipolar affective disorder-1 or those with psychotic disorders.
- Preparatory non-drug psychotherapy sessions before the experimental session
- An atmosphere of trust during the experimental session
- Close monitoring of the subject
- Daily contact with subjects for the period of 1 week after the experimental session, and availability of therapists at other times as needed.
- Non-drug integrative psychotherapy sessions
- Having subjects remain at the study site for the night of each experimental session to provide an optimal opportunity for rest and reflection following MDMA-assisted sessions, as part of the integration process.
- Availability of qualified personnel, such as a trained attendant during the overnight stay to support rest and integration of the experience.

Every effort is made to help subjects resolve difficult symptoms and to arrive at a more comfortable and relaxed state by the conclusion of the session. Such efforts include empathic listening on the part of the investigators and affect management techniques, such as diaphragmatic breathing by subjects.

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

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

    a. A psychiatric nurse, therapeutic assistant, or therapist will stay with the subject until the time of his or her appointment with investigators the next day. The investigators then meet with the subject daily until the period of destabilization has passed.
    b. If a subject experiences severe, persisting emotional distress, such as panic attacks, severe generalized anxiety, or insomnia following an MDMA session, the investigator may prescribe a drug with a short half-life as a "rescue medication." Investigators should not prescribe an SSRI, SNRI, or MAOI in this context unless it is determined that such treatment is clinically necessary and the subject will be terminated from study participation. Residual symptoms are addressed during the frequent follow-up psychotherapy visits with the investigators.
    c. Hospitalization for stabilization. If a subject should become psychotic, or if for any reason the investigators deem it necessary for safety, arrangements are made to stabilize and transfer him or her to the study site inpatient unit or the nearest appropriate inpatient psychiatric facility.

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

6.7 Abuse Potential

Despite its classification as a Schedule I drug, an examination of findings in humans and animals suggests that MDMA possesses moderate abuse potential that is higher than that reported for "classic hallucinogens" like psilocybin, but lower than that reported for psychostimulants, such as cocaine or methamphetamine. Studies assessing prevalence of problematic Ecstasy use or dependence suggest that a small percentage of individuals, especially those with prior psychological difficulties, may develop problematic Ecstasy use or dependence. In two published studies of MDMA-assisted psychotherapy for people with PTSD, only one of 32 subjects reported

using Ecstasy subsequent to study participation, and several subjects volunteered that they would not seek out Ecstasy outside of a psychotherapeutic setting. Diversion is not an issue for sponsor-supported studies because MDMA will only be administered under the supervision of the clinical investigator and no take-home doses are permitted. MDMA is handled following all regulations pertaining to the handling and dispensing of controlled substances within research studies.

7.0 Conclusion

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

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

8.0 References

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9.0 Appendix

Table 31: Percentage of Observations of Spontaneously Reported Reactions During Experimental Sessions in Studies MP-1, MP-2, MP-4, MP-8, MP-9, MP-12, MDA-1, MAA-1, and MP1-E2 as of 01 October 2015

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Sessions	24	19	15	11	14	255	4
Anxiety							
Mild	1 (4%)	---	---	2 (18%)	4 (29%)	48 (19%)	1 (25%)
Moderate	9 (38%)	---	7 (47%)	2 (18%)	1 (7%)	61 (24%)	---
Severe	4 (17%)	---	1 (7%)	---	1 (7%)	13 (5%)	---
Total	14 (58%)	0 (0%)	8 (53%)	4 (36%)	6 (43%)	122 (48%)	1 (25%)
Diarrhea							
Mild	---	---	---	---	---	5 (2%)	---
Moderate	---	---	---	---	---	---	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (2%)	0 (0%)
Disturbance in Attention							
Mild	---	---	3 (20%)	1 (9%)	1 (7%)	28 (11%)	---
Moderate	1 (4%)	---	---	---	---	10 (4%)	---
Severe	---	---	---	---	---	---	---
Total	1 (4%)	0 (0%)	3 (20%)	1 (9%)	1 (7%)	38 (15%)	0 (0%)
Dizziness							
Mild	1 (4%)	---	1 (7%)	1 (9%)	1 (9%)	40 (16%)	2 (50%)
Moderate	1 (4%)	---	---	---	---	19 (7%)	---
Severe	---	---	---	---	---	1 (<1%)	---
Total	2 (8%)	0 (0%)	1 (7%)	1 (9%)	1 (7%)	60 (24%)	2 (50%)
Somnolence							
Mild	---	---	2 (13%)	---	1 (7%)	11 (4%)	---
Moderate	3 (13%)	---	---	---	---	8 (3%)	---
Severe	---	---	---	---	---	---	---
Total	3 (13%)	0 (0%)	2 (13%)	0 (0%)	1 (7%)	19 (7%)	0 (0%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Sessions	24	19	15	11	14	255	4
Dry Mouth							
Mild	---	1 (5%)	2 (13%)	1 (9%)	---	23 (9%)	1 (25%)
Moderate	---	---	1 (7%)	2 (18%)	---	19 (7%)	1 (25%)
Severe	---	---	---	---	---	---	---
Total	0 (0%)	1 (5%)	3 (20%)	3 (27%)	0 (0%)	42 (16%)	2 (50%)
Fatigue							
Mild	3 (13%)	4 (21%)	6 (40%)	---	2 (14%)	32 (13%)	---
Moderate	7 (29%)	---	2 (13%)	3 (27%)	2 (14%)	52 (20%)	---
Severe	---	---	---	---	---	3 (1%)	---
Total	10 (42%)	4 (21%)	8 (53%)	3 (27%)	4 (28%)	87 (34%)	0 (0%)
Headache							
Mild	5 (21%)	1 (5%)	6 (40%)	3 (27%)	10 (71%)	57 (22%)	1 (25%)
Moderate	7 (29%)	---	1 (7%)	1 (9%)	---	37 (15%)	---
Severe	---	---	---	---	---	1 (<1%)	---
Total	12 (50%)	1 (5%)	7 (47%)	4 (36%)	10 (71%)	95 (37%)	1 (25%)
Sensation of Heaviness							
Mild	---	---	---	---	---	5 (2%)	1 (25%)
Moderate	---	---	---	---	---	6 (2%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (4%)	1 (25%)
Disturbed Gait							
Mild	1 (4%)	3 (16%)	---	---	2 (14%)	35 (14%)	2 (50%)
Moderate	---	---	---	---	---	6 (2%)	---
Severe	---	---	---	---	---	---	---
Total	1 (4%)	3 (16%)	0 (0%)	0 (0%)	2 (14%)	41 (16%)	2 (50%)
Judgment Impaired							
Mild	---	---	---	---	---	1 (<1%)	---
Moderate	---	---	---	---	---	---	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Sessions	24	19	15	11	14	255	4
Irritability							
Mild	---	---	1 (7%)	---	---	3 (1%)	---
Moderate	3 (13%)	---	---	---	---	3 (1%)	---
Severe	---	---	---	---	---	---	---
Total	3 (13%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	6 (2%)	0 (0%)
Insomnia							
Mild	6 (25%)	1 (5%)	1 (7%)	---	---	21 (8%)	1 (25%)
Moderate	6 (25%)	2 (11%)	---	---	3 (21%)	31 (12%)	---
Severe	---	1 (5%)	---	---	---	6 (2%)	2 (50%)
Total	12 (50%)	4 (21%)	1 (7%)	0 (0%)	3 (21%)	58 (23%)	3 (75%)
Muscle Tightness (jaw)							
Mild	2 (8%)	1 (5%)	---	1 (9%)	4 (29%)	62 (24%)	---
Moderate	3 (13%)	---	---	2 (18%)	1 (7%)	73 (29%)	1 (25%)
Severe	---	---	---	---	---	6 (2%)	1 (25%)
Total	5 (21%)	1 (5%)	0 (0%)	3 (27%)	5 (36%)	141 (55%)	2 (50%)
Decreased Appetite							
Mild	1 (4%)	2 (11%)	3 (20%)	---	4 (29%)	63 (25%)	---
Moderate	1 (4%)	1 (5%)	---	---	---	40 (16%)	1 (25%)
Severe	---	1 (5%)	---	---	---	3 (1%)	---
Total	2 (8%)	4 (21%)	3 (20%)	0 (0%)	4 (29%)	106 (42%)	1 (25%)
Depressed Mood							
Mild	---	---	---	---	---	13 (5%)	---
Moderate	2 (8%)	1 (5%)	1 (7%)	---	1 (7%)	12 (5%)	---
Severe	---	---	---	---	---	2 (1%)	---
Total	2 (8%)	1 (5%)	1 (7%)	0 (0.0%)	1 (7%)	27 (11%)	0 (0.0%)
Muscle Tightness							
Mild	1 (4%)	---	5 (33%)	1 (9%)	1 (7%)	44 (17%)	---
Moderate	2 (8%)	---	2 (13%)	2 (18%)	2 (14%)	25 (10%)	---
Severe	---	---	---	---	---	---	---
Total	3 (13%)	0 (0%)	7 (47%)	3 (27%)	3 (21%)	69 (27%)	0 (0%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Sessions	24	19	15	11	14	255	4
Nausea							
Mild	2 (8%)	2 (11%)	1 (7%)	---	2 (14%)	34 (13%)	1 (25%)
Moderate	1 (4%)	---	2 (13%)	---	---	28 (11%)	---
Severe	---	---	---	---	---	6	---
Total	3 (13%)	2 (11%)	3 (20%)	0 (0%)	2 (14%)	68 (27%)	1 (25%)
Hypersomnia							
Mild	2 (8%)	---	1 (7%)	---	1 (7%)	3 (1%)	1 (25%)
Moderate	1 (4%)	---	---	2 (18%)	---	7 (3%)	---
Severe	---	1 (5%)	---	---	---	---	---
Total	3 (13%)	1 (5%)	1 (7%)	2 (18%)	1 (7%)	10 (4%)	1 (25%)
Nystagmus							
Mild	---	---	---	---	1 (7%)	17 (7%)	1 (25%)
Moderate	---	---	---	---	---	7 (3%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	24 (9%)	1 (25%)
Paresthesia							
Mild	---	---	1 (7%)	---	1 (7%)	11 (4%)	1 (25%)
Moderate	---	---	---	---	---	5 (2%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	1 (7%)	0 (0%)	1 (7%)	16 (6%)	1 (25%)
Hyperhidrosis							
Mild	---	---	2 (13%)	---	3 (21%)	44 (17%)	1 (25%)
Moderate	1 (4%)	---	---	---	---	19 (7%)	---
Severe	---	---	---	---	---	---	---
Total	1 (4%)	0 (0%)	2 (13%)	0 (0%)	3 (21%)	63 (25%)	1 (25%)
Restlessness							
Mild	---	1 (5%)	5 (33%)	---	3 (21%)	40 (16%)	---
Moderate	2 (8%)	---	1 (7%)	---	2 (4%)	22 (9%)	1 (25%)
Severe	---	---	---	---	---	1 (<1%)	---
Total	2 (8%)	1 (5%)	6 (40%)	0 (0%)	5 (36%)	63 (25%)	1 (25%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Sessions	24	19	15	11	14	255	4
Obsessive Rumination							
Mild	---	1 (5%)	---	---	---	10 (4%)	---
Moderate	1 (4%)	---	2 (13%)	---	---	6 (2%)	---
Severe	---	---	---	---	---	---	---
Total	1 (4%)	1 (5%)	2 (13%)	0 (0%)	0 (0%)	16 (6%)	0 (0%)
Feeling Cold							
Mild	2 (8%)	1 (5%)	7 (47%)	---	4 (29%)	47 (18%)	---
Moderate	1 (4%)	---	1 (7%)	---	2 (14%)	20 (8%)	---
Severe	---	---	---	---	---	1 (<1%)	---
Total	3 (13%)	1 (5%)	8 (53%)	0 (0%)	6 (43%)	68 (27%)	0 (0%)
Thirst							
Mild	1 (4%)	---	1 (7%)	---	---	29 (11%)	1 (25%)
Moderate	---	---	---	1 (9%)	---	14 (5%)	1 (25%)
Severe	---	---	---	---	---	---	---
Total	1 (4%)	0 (0%)	1 (7%)	1 (9%)	0 (0%)	43 (17%)	2 (50%)
Asthenia							
Mild	1 (4%)	---	---	---	---	7 (3%)	1 (25%)
Moderate	---	---	---	---	---	6 (2%)	---
Severe	---	---	---	---	---	---	---
Total	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (5%)	1 (25%)

Table 32: Spontaneously Reported Reactions on Day 1-7 After All Experimental Sessions in Studies MP-1, MP-2, MP-4, MP-8, MP-9, MP-12, MDA-1, MAA-1, and MP1-E2 as of 01 October 2015

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Observations	168	133	105	77	98	1785	21
	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)
Anxiety							
Mild	26 (15%)	4 (3%)	25 (24%)	8 (10%)	5 (5%)	239 (13%)	---
Moderate	35 (21%)	---	10 (10%)	3 (4%)	1 (1%)	172 (10%)	---
Severe	2 (1%)	---	---	---	---	24 (1%)	---
Total	63 (38%)	4 (3%)	35 (33%)	11 (14%)	6 (6%)	435 (24%)	0 (0%)
Diarrhea							
Mild	1 (1%)	---	4 (4%)	---	1 (1%)	15 (1%)	---
Moderate	---	---	---	---	---	4 (0%)	---
Severe	---	---	---	---	---	2 (0%)	---
Total	1 (1%)	0 (0%)	4 (4%)	0 (0%)	1 (1%)	21 (1%)	0 (0%)
Disturbance in Attention							
Mild	11 (7%)	---	2 (2%)	2 (3%)	---	141 (8%)	---
Moderate	11 (7%)	---	2 (2%)	2 (3%)	---	38 (2%)	---
Severe	---	---	---	---	---	3 (<1%)	---
Total	22 (13%)	0 (0%)	4 (4%)	4 (5%)	0 (0%)	182 (10%)	0 (0%)
Dizziness							
Mild	5 (3%)	6 (5%)	---	---	1 (1%)	122 (7%)	---
Moderate	---	1 (1%)	---	---	---	19 (1%)	---
Severe	---	---	---	---	---	2 (<1%)	---
Total	5 (3%)	7 (5%)	0 (0%)	0 (0%)	1 (1%)	143 (8%)	0 (0%)
Somnolence							
Mild	2 (1%)	3 (2%)	1 (1%)	---	---	2 (<1%)	---
Moderate	5 (3%)	---	---	---	---	---	---
Severe	---	---	---	---	---	---	---
Total	7 (4%)	3 (2%)	1 (1%)	0 (0%)	0 (0%)	2 (<1%)	0 (0%)
Dry Mouth							
Mild	---	---	---	1 (1%)	---	23 (1%)	1 (5%)
Moderate	---	---	---	---	---	1 (<1%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	24 (1%)	1 (5%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Observations	168	133	105	77	98	1785	21
	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)
Fatigue							
Mild	23 (14%)	16 (12%)	20 (19%)	3 (4%)	27 (28%)	245 (14%)	2 (10%)
Moderate	27 (16%)	8 (6%)	8 (8%)	4 (5%)	1 (1%)	163 (9%)	14 (67%)
Severe	1 (1%)	1 (1%)	---	---	---	13 (1%)	2 (10%)
Total	51 (30%)	25 (19%)	28 (27%)	7 (9%)	28 (29%)	421 (24%)	18 (86%)
Headache							
Mild	9 (5%)	13 (10%)	1 (1%)	3 (4%)	4 (4%)	76 (4%)	---
Moderate	5 (3%)	13 (10%)	---	3 (4%)	---	33 (2%)	---
Severe	---	---	---	---	---	3 (<1%)	---
Total	14 (8%)	26 (20%)	1 (1%)	6 (8%)	4 (4%)	112 (6%)	0 (0%)
Sensation of Heaviness							
Mild	---	1 (1%)	---	---	---	3 (<1%)	---
Moderate	---	---	---	---	---	3 (<1%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	6 (<1%)	0 (0%)
Disturbed Gait							
Mild	1 (1%)	---	---	---	---	10 (1%)	---
Moderate	---	---	---	---	---	3 (<1%)	---
Severe	---	---	---	---	---	---	---
Total	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (1%)	0 (0%)
Judgment Impaired							
Mild	---	---	1 (1%)	1 (1%)	---	7 (<1%)	---
Moderate	---	---	---	1 (1%)	---	2 (<1%)	---
Severe	---	---	---	---	---	1 (<1%)	---
Total	0 (0%)	0 (0%)	1 (1%)	2 (3%)	0 (0%)	10 (1%)	0 (0%)
Irritability							
Mild	12 (7%)	3 (2%)	5 (5%)	---	4 (4%)	69 (4%)	---
Moderate	9 (5%)	---	3 (3%)	3 (4%)	---	48 (3%)	---
Severe	---	---	---	---	---	2 (<1%)	---
Total	21 (13%)	3 (2%)	8 (8%)	3 (4%)	4 (4%)	119 (7%)	0 (0%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Observations	168	133	105	77	98	1785	21
	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)
Insomnia							
Mild	19 (11%)	17 (13%)	8 (8%)	5 (6%)	6 (6%)	158 (9%)	---
Moderate	29 (17%)	13 (10%)	9 (9%)	5 (6%)	2 (2%)	88 (5%)	---
Severe	1 (1%)	8 (6%)	1 (1%)	5 (6%)	---	8 (<1%)	---
Total	49 (29%)	38 (29%)	18 (17%)	15 (19%)	8 (8%)	254 (14%)	0 (0%)
Muscle Tightness (jaw)							
Mild	2 (1%)	---	---	6 (8%)	2 (2%)	90 (5%)	---
Moderate	1 (1%)	---	---	4 (5%)	---	20 (1%)	---
Severe	---	---	---	---	---	2 (<1%)	---
Total	3 (2%)	0 (0%)	0 (0%)	10 (13%)	2 (2%)	112 (6%)	0 (0%)
Decreased Appetite							
Mild	---	10 (8%)	2 (2%)	1 (1%)	2 (2%)	89 (5%)	---
Moderate	---	2 (2%)	---	1 (1%)	---	67 (4%)	---
Severe	---	3 (2%)	---	---	---	1 (<1%)	---
Total	0 (0%)	15 (11%)	2 (2%)	2 (3%)	2 (2%)	157 (9%)	0 (0%)
Depressed Mood							
Mild	13 (8%)	14 (11%)	4 (4%)	3 (4%)	---	114 (6%)	3 (14%)
Moderate	8 (5%)	11 (8%)	4 (4%)	---	---	101 (6%)	---
Severe	---	---	---	---	---	17 (1%)	---
Total	21 (13%)	25 (19%)	8 (8%)	3 (4%)	0 (0%)	232 (13%)	3 (14%)
Muscle Tightness							
Mild	3 (2%)	1 (1%)	3 (3%)	9 (12%)	6 (6%)	84 (5%)	---
Moderate	6 (4%)	---	---	7 (9%)	1 (1%)	26 (1%)	---
Severe	---	---	---	---	---	5 (<1%)	---
Total	9 (5%)	1 (1%)	3 (3%)	16 (21%)	7 (7%)	115 (6%)	0 (0%)
Nausea							
Mild	9 (5%)	5 (4%)	2 (2%)	1 (1%)	---	66 (4%)	---
Moderate	3 (2%)	2 (2%)	---	1 (1%)	---	28 (2%)	---
Severe	---	7 (5%)	---	---	---	4 (<1%)	---
Total	12 (7%)	14 (11%)	2 (2%)	2 (3%)	0 (0%)	98 (5%)	0 (0%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Observations	168	133	105	77	98	1785	21
	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)
Hypersomnia							
Mild	15 (9%)	8 (6%)	9 (9%)	3 (4%)	17 (17%)	145 (8%)	2 (10%)
Moderate	9 (5%)	7 (5%)	1 (1%)	3 (4%)	---	63 (4%)	---
Severe	---	---	1 (1%)	---	---	---	---
Total	24 (14%)	15 (11%)	11 (10%)	6 (8%)	17 (17%)	208 (12%)	2 (10%)
Nystagmus							
Mild	---	---	---	---	---	1 (<1%)	---
Moderate	---	---	---	---	---	---	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Paresthesia							
Mild	---	---	---	---	---	4 (<1%)	---
Moderate	---	---	---	---	---	4 (<1%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (<1%)	0 (0%)
Hyperhidrosis							
Mild	1 (1%)	---	---	---	1 (1%)	13 (1%)	---
Moderate	---	---	---	1 (1%)	---	1 (<1%)	---
Severe	1 (1%)	---	---	---	---	---	---
Total	2 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	14 (1%)	0 (0%)
Restlessness							
Mild	---	2 (2%0	1 (1%)	3 (4%)	---	24 (1%)	---
Moderate	---	---	---	2 (3%)	---	24 (1%)	---
Severe	---	---	---	---	---	5 (<1%)	---
Total	0 (0%)	2 (2%)	1 (1%)	5 (6%)	0 (0%)	53 (3%)	0 (0%)
Obsessive Rumination							
Mild	2 (1%)	6 (5%)	2 (2%)	4 (5%)	1 (1%)	37 (2%)	---
Moderate	6 (4%)	1 (1%)	---	2 (3%)	---	38 (2%)	---
Severe	---	---	---	---	---	5 (<1%)	---
Total	8 (5%)	7 (5%)	2 (2%)	6 (8%)	1 (1%)	80 (4%)	0 (0%)

Dose	0 mg (N=12)	25 mg (N=7)	30 mg (N=7)	40 mg (N=6)	75 mg (N=7)	100-125 mg (N=100)	150 mg (N=3)
Observations	168	133	105	77	98	1785	21
	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)	Counts (%)
Feeling Cold							
Mild	---	2 (2%)	2 (2%)	---	---	26 (1%)	---
Moderate	---	---	---	---	---	7 (<1%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	2 (2%)	2 (2%)	0 (0%)	0 (0%)	33 (2%)	0 (0%)
Thirst							
Mild	---	---	---	1 (1%)	---	7 (<1%)	---
Moderate	---	---	---	---	---	1 (<1%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	8 (<1%)	0 (0%)
Asthenia							
Mild	---	---	1 (1%)	---	---	20 (1%)	---
Moderate	---	---	---	1 (1%)	---	11 (1%)	---
Severe	---	---	---	---	---	---	---
Total	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	31 (2%)	0 (0%)

APPENDIX B

US v. Phan (W.D. WA 2011), Supplemental Sentencing Memorandum ("*Phan* memo")

THE HONORABLE RICARDO S. MARTINEZ

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON

UNITED STATES OF AMERICA, Plaintiff, v. TRUNG DINH PHAN, Defendant.	CR10-00027-RSM DEFENDANT PHAN'S SUPPLEMENTAL SENTENCING MEMORANDUM ADDRESSING THE APPROPRIATE GUIDELINE

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Other Authorities: Usage and Medical Data (available online or as Exhibits)

PRELIMINARY STATEMENT

This Supplemental Sentencing Memorandum is respectfully submitted in advance of Defendant Trung Phan's sentencing, currently scheduled for January 21, 2011. This Memorandum is not exhaustive in that it does not address Mr. Phan's personal characteristics as they relate to 18 U.S.C. § 3553(a). Instead, it supplements the Sentencing Memorandum of co-counsel, the Federal Public Defender, by speaking to one particular issue of critical importance to Mr. Phan's sentencing: the appropriateness of adhering to the empirically-flawed U.S. Sentencing Guideline for MDMA (hereinafter "MDMA Guideline").

The MDMA Guideline was established nearly ten years ago in response to public panic and is based on faulty science that has since been repudiated. When the Sentencing Commission created the MDMA Guideline in 2001, it crafted a penalty structure based on the conclusion that MDMA was more harmful than cocaine and in light of what the Commission viewed as the pharmacological and physiological harms of the drug. Subsequent studies have substantially undercut scientific support for the Commission's conclusion that MDMA is more harmful than cocaine, as well as the Commission's assessment of the harms of MDMA. Cocaine use is not only much more prevalent in the United States population, but according to recent government data, it is thirteen times more likely to cause a user to visit an emergency room. As for the harms of MDMA itself, recent research reveals that the harms are relatively mild and reversible rather than severe and long-lasting. Scientists have discovered that most of the research from ten years ago was flawed. For example, animal studies overestimated the harms of MDMA

to humans because they gave animals doses several times higher than the average human dose. Human studies failed to control for important variables such as the use of other drugs and propensity toward mental illness.

Under *Kimbrough v. United States*, 552 U.S. 85 (2007), this Court has discretion to vary from Guidelines that lack an empirical basis. Because the MDMA Guidelines are seriously flawed, as discussed in detail below, this Court should exercise that discretion here. Failure to do so would result in a grave injustice, adding unnecessary years onto a sentence based on long-discredited myths about the harmfulness of the offense. When the Supreme Court in *Kimbrough* recognized sentencing courts' power to depart from Guidelines that lack an empirical basis, this is precisely the type of case the Court had in mind. Like the crack cocaine Guideline at issue in *Kimbrough*, the MDMA Guideline is scientifically unsupportable and, as a result, prescribes sentencing ranges that are unfairly severe. This Court should exercise its sound discretion under *Kimbrough* to avoid blindly following a Guideline that offers no legitimate guidance. Instead, it should look beyond the faulty data that the Commission relied on in 2001, and determine an appropriate initial sentencing range for Mr. Phan that is based on consideration of the scientifically-documented properties and harms of MDMA.[1]

[1] As the Court is aware, the Court's final task, after consideration of the applicable Guideline, is to make "an individualized assessment based on the facts presented" in light of the sentencing factors Congress has set forth in 18 U.S.C. § 3553(a). *Gall v. United States*, 552 U.S. 38, 49-50 (2007). The application of these factors is addressed as part of the defense's separate memorandum filed by co-counsel from the Federal Public Defender.

ARGUMENT

I. THIS COURT HAS DISCRETION TO VARY DOWNWARD FROM THE OTHERWISE-APPLICABLE GUIDELINE RANGE WHEN THE COMMISSION HAS ABANDONED ITS TRADITIONAL ROLE BY DEVELOPING GUIDELINES THAT LACK AN EMPIRICAL BASIS.

The Supreme Court has held that where a particular Guideline is not based on empirical evidence, it is not an abuse of discretion for a district court to impose an outside-of-Guidelines sentence based solely on broad policy concerns. *Kimbrough v. United States*, 552 U.S. 85, 108-10 (2007). Thus, for example, a district court is free to impose a significant downward variance even in a mine-run case (an average case with no distinguishing circumstances or offender characteristics bearing on sentencing) involving crack cocaine, based on the district court's policy disagreement with the 100-to-1 crack-powder disparity embodied in the Guidelines. *See id.* at 110.

In *Kimbrough*, the Supreme Court noted that "Congress established the commission to formulate and *constantly refine* national sentencing standards." *Id.* at 108 (citation and internal quotation marks omitted and emphasis added). The Court has elaborated that "[t]he Commission's work is ongoing. The statutes and the Guidelines themselves foresee continuous evolution helped by the sentencing courts and courts of appeals in that process." *Rita v. United States*, 551 U.S. 338, 350 (2007). Moreover, the Court left no doubt that the district courts are at the forefront of this evolutionary process, and may take initiative on sentencing matters well before the Sentencing Commission alters the guidelines themselves:

> The sentencing courts, applying the Guidelines in individual cases may depart (either pursuant to the Guidelines or, since *Booker*, by imposing a non-guidelines sentence). The judges will set forth their reasons. The Courts of Appeals will determine the reasonableness of the resulting sentence. The Commission will collect and examine the results. In doing so, it may obtain advice from prosecutors, defenders, law enforcement groups, civil liberties associations, experts in penology, and others. And it can revise the Guidelines accordingly.

Id. As our empirical understanding about the science of MDMA evolves, and as our national experience changes, the MDMA Guideline should change with them.

Kimbrough's holding permitting judges to vary from Guideline ranges based on policy disagreements extends beyond cases involving crack cocaine and permits Guideline variances in other criminal matters involving non-empirically derived Guidelines, including those involving other drugs. Federal courts have cited *Kimbrough* as authority for policy-based departures from Guidelines for drugs other than crack. *See, e.g.*, *United States v. Valdez*, 268 Fed. App'x 293, 297 (5th Cir. 2008) (mem.) (methamphetamine); *United States v. Goodman*, 556 F. Supp. 2d 1002, 1010-11, 1016 (D. Neb. 2008) (methamphetamine); *United States v. Thomas*, 595 F. Supp. 2d 949, 952 (E.D. Wis. 2009) (powder cocaine). In fact, the Supreme Court has implied that its reasoning in *Kimbrough* could apply to *all* drug Guidelines, since "the Sentencing Commission departed from the empirical approach when setting the Guidelines range for drug offenses." *Gall v. United States*, 552 U.S. 38, 46 n.2 (2007).

Federal courts even depart from Guidelines for other types of offenses entirely. *See, e.g., United States v. Cavera*, 550 F.3d 180, 184 (2nd Cir. 2008) (en banc) (arms trafficking); *United States v. Herrera-Zuniga*, 571 F.3d 568, 583, 586 (6th Cir. 2009)

(illegal reentry); *United States v. Vanvliet*, 542 F.3d 259, 271 (1st Cir. 2008) (interstate travel with the intent to engage in an illicit sexual act); *United States v. Baird*, 580 F. Supp. 2d 889, 894-95 (D. Neb. 2008) (child pornography). In these cases — and in many more — appellate and sentencing courts have recognized that district courts have authority to depart from any Guideline that was not based on reasoned, empirical evidence.

In an illuminating recent decision holding that the imposition of a 240-month sentence for distributing child pornography, while procedurally correct under the Guidelines, was substantively unreasonable, the Second Circuit discussed appropriate considerations for determining how much credence to lend any particular Guideline:

> The Sentencing Commission is, of course, an agency like any other. . . . [In today's advisory-Guideline regime,] deference to the Guidelines is not absolute or even controlling; rather, like our review of many agency determinations, "[t]he weight of such a judgment in a particular case will depend upon the thoroughness evident in [the agency's] consideration, the validity of its reasoning, its consistency with earlier and later pronouncements, and all those factors which give it power to persuade, if lacking power to control."

United States v. Dorvee, 616 F.3d 174, 187-88 (2nd Cir. 2010) (quoting *Skidmore v. Swift & Co.*, 323 U.S. 134, 140 (1944)). The *Dorvee* court further instructed courts to take account of the Commission's "'*specialized experience* and broader investigations and *information available to the agency*'" when determining the weight owed to a Guideline. *See id.* at 188 (quoting *United States v. Mead Corp.*, 533 U.S. 218, 234 (2001)) (emphasis added).

Although the Commission heard statements from multiple scientists when revising the MDMA Guideline in 2001, no one on the Commission had any greater expertise in weighing that evidence than this Court does. During the 2001 public hearing on the proposed MDMA Guideline, Commissioner Michael E. O'Neill observed that:

> Part of the difficulty, I suppose, that we're having is, we've been able to read and have had a lot of different scientific evidence presented to us. And since none of us is a scientist that I'm aware of, it's sometimes difficult to digest this information.[2]

Given the lack of scientific expertise of the Commission, it is evident that it did not have the specialized experience that the *Dorvee* court indicated would add weight to its findings. Additionally, the "information available to the agency," *Dorvee*, 616 F.3d at 188, regarding MDMA in 2001 was at best incomplete and at worst rife with inaccuracy and myth. As discussed in detail in Part II below, years of additional scientific research since the formulation of the current Guideline have undermined assumptions central to the Commission's decisions in 2001 and provide this Court with access to far more reliable data than was available to the Commission when it set the MDMA guideline almost ten years ago. Accordingly, this Court should not defer to the findings of the Commission, but instead should make its own determination as to the appropriate offense level and sentence.

The published information discussed in detail below should be more than sufficient basis for this Court to conclude that the current MDMA Guideline is flawed

[2] U.S. Sentencing Comm'n, *Tr. of U.S. Sentencing Comm'n 2001 Public Hearing* 26 (Mar. 19, 2001).

and that another, lower range should be used as a baseline. However, if this Court would like to hear directly from the leading experts in the field, we encourage the Court to hold an evidentiary hearing to consider in greater detail the new scientific developments since the Commission's actions in 2001. *See, e.g., United States v. Grober*, 624 F.3d 592, 595 (3d Cir. 2010) (affirming sentencing varying from child pornography guideline after district court held extensive evidentiary hearing on the background and formulation of the relevant guideline).

Another district court considering the scientific validity of the MDMA Guideline has held just such a hearing. *See United States v. McCarthy*, No. 09 Cr. 1136 (WHP) (S.D.N.Y.). In this hearing, the sentencing court took two days' worth of testimony from expert witnesses, two from the government and two from the defense. Although that court's decision whether to vary from the MDMA Guideline remains pending, the transcript of that hearing (hereinafter referred to as the "New York hearing" and cited as "N.Y. Hrg. Tr.") may be illuminating for this Court and therefore is attached as an exhibit.[3] The hearing is notable for the extent of agreement among the experts about the actual harms of MDMA. Although the defense and government experts characterized the state of the field differently, the substance of the two sides' key conclusions reflected significant congruence. Therefore the New York transcript will be cited below where relevant. Courtesy copies of all additional scientific, journalistic or government sources cited in this memorandum and not easily accessible online will be provided to the Court.

[3] *See* Ex. 1, *United States v. McCarthy*, No. 09 Cr. 1136 (WHP) (S.D.N.Y. Dec. 6-7) (transcript of evidentiary hearing) [hereinafter Ex. 1, N.Y. Hrg. Tr.].

II. LIKE THE CRACK COCAINE GUIDELINE AT ISSUE IN *KIMBROUGH*, THE MDMA GUIDELINE LACKS AN EMPIRICAL BASIS BECAUSE IT IS BASED ON NOW-DISCREDITED SCIENCE.

New studies have discredited the decade-old science underlying the Commission's formulation of the Guideline for MDMA sentences. This Court should therefore place the MDMA Guideline in the same category as the crack cocaine Guideline — namely, instances in which the Commission was not acting in its traditional role. *Kimbrough*, 552 U.S. at 108-110. The Commission did not consider past sentencing practices when formulating the current MDMA Guideline. Rather, as with the crack cocaine Guideline that the Supreme Court considered in *Kimbrough*, the MDMA Guideline reflects the Sentencing Commission's response to a congressional directive issued in the midst of an uninformed panic about a supposed new drug scourge. With the benefit of hindsight, it is clear that the Commission's conclusions about the harmfulness of MDMA — and in particular the Commission's conclusion that MDMA is more harmful than cocaine — are simply incorrect and do not comport with empirical evidence and national experience.

There are strong parallels between the formulation of the MDMA Guideline and the development of the crack cocaine Guidelines. The Commission set the Guidelines for both substances in response to congressional directives, rather than empirical evidence about past sentencing practices. *See Kimbrough*, 552 U.S. at 96-97 (describing development of the crack cocaine Guidelines based on the notorious 100-to-1 crack-powder disparity); MDMA Anti-Proliferation Act, Pub. L. No. 106-310 (2000) (ordering increased penalties for MDMA). Just as crack cocaine in the 1980s became associated

in the national consciousness with violence, addiction and overdose, the sudden appearance of MDMA among teenagers and the development of a new "rave culture" in the late 1990s sparked a similar panic.[4] The potential harms from MDMA were so drastically forecast that Congress directed the Commission to promulgate an "emergency amendment" to the MDMA Guideline, and the Commission, in its haste to respond, "shifted resources from other important policy development areas, such as implementing other congressional directives regarding stalking and sexual offenses against children."[5]

It was in this context that the Commission amended the Drug Equivalency Tables in U.S.S.G. 2D1.1 to increase sentences for MDMA dramatically: as reflected in the Sentencing Commission's report to Congress explaining the 2001 MDMA amendment, prior to the amendment, one gram of MDMA was treated as equivalent to 35 grams of marijuana; the 2001 amendment set one gram of MDMA equal to 500 grams of marijuana.[6] As a result, the length of the average MDMA sentence more than doubled.[7]

This change was not the product of careful empirical investigation but rather reliance on sloppy studies that dramatically overstated the harms of MDMA. In 2001, little work had been done regarding MDMA's effects on humans, and there were no well-controlled studies that followed human users over time.[8] In the absence of such empirical

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[4] *See* Rosenbaum, *Ecstasy: America's New "Reefer Madness," Journal of Psychoactive Drugs* 3 (Apr.-Jun. 2002); *Guidelines Stiffened for Selling MDMA*, Assoc. Press, Mar. 21, 2001 (quoting the acting director of the Office of National Drug Control Policy: "We never again want another 'crack epidemic' to blindside this nation.").

[5] *Hearing on MDMA Abuse Before the S. Comm. On Int'l Narcotics Trafficking*, 107th Cong. (2001) (statement of Diana E. Murphy, Chair of the U.S. Sentencing Commission), at 1.

[6] U.S. Sentencing Comm'n, *Report to Congress: MDMA Drug Offenses, Explanation of Recent Guideline Amendments* 5-6 (2001) [*hereinafter* "MDMA Report"].

[7] *See id.* at 6 (noting increase in average sentence from just under 3 years to just over 6 years).

[8] *See* Ex. 1, N.Y. Hrg. Tr. at 23 (Curran, defense expert); *id.* at 376 (Hanson, government expert) (agreeing that "the field is fairly new in terms of psychpharmacologists absolutely isolating the effects of MDMA alone").

data, the Commission formulated the current MDMA Guideline by comparing MDMA to two quite harmful drugs, heroin and cocaine, and deciding that MDMA fell in between them in terms of harmfulness.[9] As a result of the Commission's conclusion that MDMA is more harmful than cocaine, the Commission set one gram of MDMA equivalent to 2.5 grams of cocaine for purposes of sentencing.[10]

With the benefit of hindsight, we can conclude with confidence today that the Commission's comparison to cocaine was faulty on several levels. First, to the extent it is possible to compare the drugs directly in terms of their harmfulness — by looking to data about drug-related emergency room visits, and by looking to the opinions of scientific experts — MDMA emerges as far less harmful than cocaine. Second, to the extent the Commission's findings were based on, in the Commission's words, "the unique pharmacological and physiological harms of ecstasy,"[11] recent studies have undercut the scientific support for the Commission's understanding of these harms. The scientific data on MDMA ten years ago was rife with errors, such as mistranslating human doses to animal doses and failure to control for key variables, and some of the Commission's scientific sources and conclusions are questionable even on their face. More recent studies show that the harms of MDMA are far less serious than posited by the Commission. Finally, to the extent the Commission relied on fears of a dramatic rise in youth use of MDMA as compared with cocaine, the trends cited by the Commission have not been borne out in the intervening decade.

[9] MDMA Report, at 5.
[10] *See id.* (setting one gram of MDMA equivalent to 500 grams of marijuana, and noting one gram of cocaine is equivalent to 200 grams of marijuana).
[11] *Id.*

A. Contrary To The Commission's Central Conclusion, MDMA Is Not More Harmful Than Cocaine.

Whether judging by medical data or the views of scientific experts, the Commission was clearly wrong to conclude that MDMA is more harmful than cocaine.

i. Medical data

The simplest way to compare the harms of drugs is to look at how frequently each leads to serious medical consequences. Although emergency-room visits is not a perfect proxy, this is a measure that does reflect serious harm; it is a measure for which there is reliable government data; and it is a measure that the Commission itself thought relevant enough to cite in its 2001 Report on MDMA.[12] In the New York hearing, experts for both the defense and the government acknowledged the relevance of this data to an assessment of the harms of MDMA.[13]

Each year, the Substance Abuse and Mental Health Services Administration of the federal Department of Health and Human Services compiles data on drug-related emergency room visits, and breaks down each drug-related visit by which drug or drugs were involved according to medical records. The most recent years for which such data are available are 2006 and 2007. The Department of Health and Human Services also compiles data on overall national drug use rates.

From this data, two conclusions stand out starkly. First, on a yearly basis cocaine is abused by two to three times as many Americans as is MDMA. Second, even accounting for the differential rates of use in the population, cocaine far exceeds MDMA

[12] *See id.* at 11 n. 28.
[13] *See* Ex. 1, N.Y. Hrg. Tr. at 125 (Halpern, defense expert); *id.* at 291 (Parrott, government expert); *id.* at 372-74 (Hanson, government expert).

as a cause of drug-related emergency-room visits: a cocaine user is approximately 13 times more likely to require drug-related emergency services than an MDMA user.

According to data from the Department of Health and Human Services' National Survey on Drug Use and Health ("NSDUH"),[14] in 2006 and 2007 (the years covered by the latest emergency room data), fewer Americans used MDMA than cocaine. In 2006, approximately 6.1 million people reported using cocaine within the previous year; the number of people reporting using ecstasy during the same time period was approximately 2.1 million.[15] In 2007, similarly, approximately 5.7 million people reported using cocaine within the previous year; the number of people reporting using ecstasy during the same time period was once again approximately 2.1 million.[16]

However, the difference in emergency room visits for each drug far outstrips the difference in usage rates. The NSDUH statistics cited above reflect that two-and-a-half to three times as many people used cocaine as used MDMA in 2006 and 2007. By contrast, in 2006, cocaine was the cause of approximately *thirty-three* times as many emergency room visits as MDMA.[17] In 2007 (the most recent year for which data are available), cocaine accounted for *forty-two* times as many emergency room visits as

[14] Ex. 2, U.S. Dep't of Health & Human Servs., Substance Abuse & Mental Health Servs. Admin., *Nat'l Survey on Drug Use and Health* [hereinafter "Ex. 2, NSDUH"], *available at* http://www.oas.samhsa.gov/nsduh.htm. The website for this study is quite extensive and difficult to navigate, so the relevant tables are attached as Exhibit 2.
[15] *See id.*, tbl. 1.1A ("Types of Illicit Drug Use in Lifetime, Past Year, and Past Month among Persons Aged 12 or Older: Numbers in Thousands, 2006 and 2007").
[16] *See id.*
[17] *See* U.S. Dep't of Health & Human Servs., Substance Abuse & Mental Health Services Admin., *Drug Abuse Warning Network 2006: Nat'l Estimates of Drug-Related Emergency Department Visits* [hereinafter "DAWN 2006"] 20 (2008), *available at* https://dawninfo.samhsa.gov/files/ED2006/DAWN2k6ED.pdf.

MDMA.[18] Thus, the emergency room statistics show that cocaine is far more harmful than MDMA not only across the population as a whole but also among the respective populations that use each drug.

Put in rough numerical terms, out of the approximately 5.9 million individuals who used cocaine, on average, per year in 2006 and 2007, approximately 551,000 individuals, or approximately 9.3% (551,000 ÷ 5,900,000), on average, went to the emergency room in connection with the drug.[19] By contrast, out of the approximately 2.1 million individuals who used MDMA, on average, per year in 2006 and 2007, approximately 15,000 individuals, or approximately 0.7% (15,000 ÷ 2,100,000), on average, went to the emergency room in connection with the drug.[20] Therefore a cocaine user was more than 13 times (9.3 ÷ 0.7) more likely than an MDMA user to require drug-related emergency services.

Another simple way to put the two drugs in perspective is to note that cocaine, which accounts for almost 30% of all drug-related visits to the emergency room (including visits stemming from legal drugs as well as illegal drugs), is the leading cause of drug-related visits to the emergency room, whereas MDMA leads to less than 1% of

[18] *See* U.S. Dep't of Health & Human Servs., Substance Abuse and Mental Health Services Admin., *Drug Abuse Warning Network 2007: Nat'l Estimates of Drug-Related Emergency Department Visits* 22 [hereinafter "DAWN 2007"] (2010), *available at* https://dawninfo.samhsa.gov/files/ED2007/DAWN2k7ED.pdf.

[19] For the number of users, see Ex. 2, NSDUH, tbl. 1.1A. The 5.9 million figure is an approximate average of the 2006 number, 6,069,000, and the 2007 number, 5,738,000. For the number of emergency room visits, see DAWN 2006, at 20, and DAWN 2007, at 22. The 551,000 figure is an approximate average of the 2006 number, 548,608, and the 2007 number, 553,530.

[20] For the number of users, see Ex. 2, NSDUH, tbl. 1.1A. The 2.1 million figure is an approximate average of the 2006 number, 2,130,000, and the 2007 number, 2,132,000. For the number of emergency room visits, see DAWN 2006, at 20, and DAWN 2007, at 22. The 15,000 figure is an approximate average of the 2006 number, 16,749, and the 2007 number, 12,748.

drug-related visits.[21] In fact, more than twice as many people are hospitalized annually because of adverse reactions to acetaminophen (the active ingredient in Tylenol) as MDMA ingestion.[22]

ii. Expert opinion

In the New York hearing, experts for both the government and the defense agreed that cocaine was more harmful than MDMA.[23]

Three European surveys of scientific and health-policy experts also support the conclusion that MDMA is less harmful than cocaine. In two studies in the prominent British medical journal *The Lancet* (including one just last year) that assessed the relative harmfulness of twenty substances of abuse based on the harmfulness of the drug to the individual user and to society, MDMA ranked among the bottom four out of twenty in both studies, whereas cocaine ranked among the top five in both studies.[24] For two other comparison points, marijuana and ketamine (which the Guidelines treat as equivalent to marijuana for sentencing purposes[25]) also ranked as more harmful than MDMA: marijuana ranged between sixth and eighth, and ketamine ranked eleventh in both studies.[26]

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[21] DAWN 2007, at 22.

[22] *Compare*, *Ban is Advised on Top Two Pills for Pain Relief*, N.Y. Times, Jul. 1, 2009, at A1 (42,000 hospitalized for acetaminophen annually), *with* DAWN 2007, at 22 (12,748 hospitalized for MDMA in 2007), *and* DAWN 2006, at 20 (16,749 hospitalized for MDMA in 2006).

[23] *See* Ex. 1, N.Y. Hrg. Tr. at 127 (Halpern, defense expert); *id.* at 231-32 (Parrott, government expert). The government's other expert, Glen Hanson, refused to compare the two drugs directly because they were in his view "apples and oranges." *Id.* at 343 (Hanson); *see also id.* at 338. However, he did acknowledge that, by the metric of emergency-room visits, MDMA is less harmful. *See id.* at 373-74.

[24] *See* Nutt et al., *Development of a rational scale to assess the harm of drugs of potential misuse*, 369 The Lancet 1047, 1051 (2007); Nutt et al., *Drug harms in the UK: a multicriteria decision analysis*, 376 The Lancet 1558, 1561 (2010).

[25] U.S.S.G. § 2D1.1, app. note 10(E), at 543 (2009).

[26] *See* Nutt 2007, 369 The Lancet at 1049-50; Nutt 2010, 376 The Lancet at 1561.

A 2010 study conducted by prominent Dutch researchers arrived at results similar to those published in *The Lancet*.[27] The Dutch study's aggregate harm scores for cocaine's individual and social harm were almost twice those for MDMA.[28] Powder cocaine was ranked sixth on its list of harmful drugs and MDMA was fourteenth.[29] Marijuana and ketamine were both ranked as more harmful than MDMA.[30]

In sum, whether one looks at the emergency room data documenting the actual consequences of MDMA use and cocaine user, or the consensus view among scientific experts about the relative harmfulness of each drug, it is clear that the Commission was incorrect in its central conclusion that MDMA is more harmful than cocaine. This faulty assumption should not continue to drive the sentences of MDMA offenders long after it has been disproved by medical data and abandoned by scientists.

B. The Commission's 2001 Report Is Rife With Methodologically Suspect Or Subsequently Disproved Research

The Commission's scientific evidence exhibits many of the problems endemic to the MDMA field ten years ago: inadequate controls, inappropriate doses, and non-replicable studies. Specifically, when considering the guidelines for MDMA, the Commission's "empirical data" included case studies of individuals who were heavy users of other drugs; studies in which animals were administered doses that we now know are exponentially larger relative to their size than doses human beings ingest; a website that the Commission itself noted was not scientific; and the work of a researcher who

[27] van Amsterdam et al., *Ranking the Harm of Alcohol, Tobacco and Illicit Drugs for the Individual and the Population*, 16 Eur. Addiction Research 202, 204 (2010).
[28] *Id.*
[29] *Id.*
[30] *Id.*

subsequently retracted multiple MDMA studies because he was testing the wrong chemical compound. These and other empirical shortcomings of the Commission's work should leave this Court profoundly skeptical of the resulting MDMA Guideline.

i. Inadequate controls

To document the purported fact that MDMA is "used compulsively by some" and "may produce dysphoria" (i.e., depression)[31] the Commission cited a paper documenting three case studies. This paper is emblematic of problems that plagued the field of MDMA science at that time, when many published papers failed to control for important variables.[32]

The subjects of the studies were, respectively, a heavy user of cocaine and marijuana, a heroin user with a family history of schizophrenia, and a PTSD patient who also consumed a bottle of Jack Daniels almost every night.[33] The failure to control for the important variables of simultaneous use of drugs other than MDMA, preexisting conditions, and family history, make it impossible to isolate the effects of MDMA in these case studies.[34] The Commission's reliance on this type of paper for its conclusions illustrates both the underdeveloped state of MDMA research in 2001 and the use of problematic source material by the Commission in setting the current Guideline.

[31] MDMA Report, at 18.
[32] *See* Ex. 1, N.Y. Hrg. Tr. at 118-20 (Halpern, defense expert); *id.* at 178 (Parrott, government expert); *id.* at 331 (Hanson, government expert).
[33] MDMA Report, at 18 n. 61 (citing Jansen, *Ecstasy (MDMA) Dependence*, 53 Drug & Alc. Dependence 121-24 (1999)).
[34] *See* Ex. 1, N.Y. Hrg. Tr. at 39-40 (Curran, defense expert); *id.* at 234-36, 239-41 (Parrott, government expert).

ii. Inappropriate dosage levels

Another major flaw in the MDMA research that dominated the scientific discourse a decade ago is the use of inappropriately high doses in animal studies to predict consequences for human users. Specifically, the Commission's 2001 Report relies on two papers that adhere to the view that monkeys and rats should be given multiples of a normal human dose in order to determine how a human would react to a normal human dose.[35] But the validity of this theory has been repudiated by newer studies that suggest the doses used in early animal studies were far too high.[36] For example, the Commins study cited by the Commission gave rats between 10 and 40 milligrams of MDMA per kilogram of body weight (expressed in scientific terms as "mg/kg"),[37] whereas recent research suggests an appropriate dose would be between 1 and 3 mg/kg.[38] Thus, the Commission relied on a study giving rats a dose equivalent to between *three and forty times* a normal human dose. More recent animal studies that have used more moderate dosage or self-administration have found little or no evidence of harm.[39]

In the New York hearing, experts for both the defense and the government acknowledged the importance of, and agreed with, recent scientific work calling into

[35] *See* MDMA Report, at 9 n.16 (citing Ricaurte et al., *(+/-) 3,4-methylenedioxymethamphetamine ('Ecstasy')-induced neurotoxicity: studies in animals*, 42 Neuropsychobiology 5-10 (2000), and Commins et al., *Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain*, 241 J. of Pharm. & Experimental Therapeutics 338-345 (1987)).

[36] *See, e.g.*, Baumann et al., *3,4-Methylenedioxymethamphetamine (MDMA) Neurotoxicity in Rats: A Reappraisal of Past and Present Findings*, 189 Psychopharmacology (Berl.) 407, 411 (2007); Green et al., *MDMA: On the Translation from Rodent to Human Dosing*, 204 Psychopharmacology 375, 375 (2009).

[37] *See* Commins et al., *Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain*, 241 J. of Pharm. & Experimental Therapeutics 338, 339 (1987).

[38] *See, e.g.*, Baumann, 189 Psychopharmacology (Berl.) at 411-13.

[39] *See, e.g.*, Fantegrossi et al., *Behavioral and Neurochemical Consequences of Long-term Intravenous Self-administration of MDMA and its Enantiomers by Rhesus Monkeys*, 29 Neuropsychopharmacology 1270, 1278-79 (2004); Wang et al., *Methylenedioxymethamphetamine Administration to Rats Does Not Decrease Levels of the Serotonin Transporter Protein or Alter its Distribution Between Endosomes and the Plasma Membrane*, 314 J. Pharmacol. Exp. Ther. 1002, 1011 (2005).

question the older principles of dose-conversion between species.[40] In fact, both of the government's experts acknowledged that 1-3 mg/kg represents the dose an average or recreational user would consume,[41] and that low to moderate use was "consistent with a typical recreational ecstasy user"[42] whereas heavy use was "rare."[43] Obviously, a substance that might have moderate effects at a low dose can have much more serious effects at a higher dose.[44] The Commission's reliance on old, inaccurate assumptions about dosing levels undercuts the validity of its conclusions.

iii. Non-replicable studies and dubious assumptions

The Commission also relied on several studies that were not able to be replicated, or scientists whose work was fraught with methodological problems. For instance, Dr. George Ricaurte, cited and relied upon as "[a] leading researcher in MDMA toxicity studies" in the Commission's 2001 report to Congress,[45] had to retract multiple studies after it was discovered that they had not been done with MDMA, but with mislabeled vials of methamphetamine. After this error came to light, in 2003 the journal *Science* retracted a Ricaurte study purporting to show that a single dose of MDMA could cause brain injury.[46] The mislabeled vials corrupted several of Ricaurte's other studies, as well, and he was forced to withdraw four other papers.[47] Even scientists Ricaurte named in defense of his work were quoted in the *New York Times* as saying that "some of his best-

[40] *See* Ex. 1, N.Y. Hrg. Tr. at 120 (Halpern, defense expert); *id.* at 355-57 (Hanson, government expert).
[41] *See id.* at 299-300 (Parrott, government expert); *id.* at 356 (Hanson, government expert).
[42] *See id.* at 352 (Hanson, government expert).
[43] *See id.* at 272 (Parrott, government expert).
[44] *See id.* at 265-66 (Parrott, government expert).
[45] MDMA Report, at 8.
[46] *See* McNeil, *Research on Ecstasy Is Clouded By Errors*, N.Y. Times, Dec. 2, 2003 at F1.
[47] *Id.*

known work has nonetheless been 'sloppy' or 'not as methodologically rigorous as you might want.'"[48]

In other areas, the Commission cited research that more recent studies with better technology have called into question. For example, the Commission referred to a study showing loss of serotonin transporters (an important neurotransmitter) "throughout the brain," and for this conclusion the Commission relied on a 1998 brain scan study by McCann and colleagues.[49] But a 2010 article in the journal *Brain*, Kish and colleagues, using more advanced technology developed over the past dozen years, found that loss of serotonin transporters was much less prevalent than had been thought and, in explicit contrast to the McCann study, noted that the new study "did not find a global, massive reduction of brain [serotonin transporter] binding."[50] A 2009 study suggested that what reduction in serotonin transporters does occur is reversible after users abstain from use — in other words, after users stop using, their brains return to normal.[51]

And some of the Commissions' authorities and claims are suspect on their very face. For example, at one point in its Report to Congress, the Commission cited, as an authority regarding purported MDMA harms, a website that the Commission itself noted consisted of "a mix of science, pseudo-science and lore."[52] In another instance, the Commission suggests that MDMA must be more harmful than cocaine because MDMA

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[48] *Id.* at F2.
[49] MDMA Report, at 9 & n.18 (citing Mathias, NIDA Notes, *"Ecstasy" Damages the Brain and Impairs Memory in Humans*, Pub. No. 99-3478 (Nov. 1999), in turn citing McCann et al., *Positron emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings*, 352 The Lancet 1433 (1998)).
[50] Kish et al., *Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[^{11}C]DASB and structural brain imaging study*, 133 Brain 1779, 1791 (2010).
[51] Selveraj et al., *Brain serotonin transporter binding in former users of MDMA ('ecstasy')*, 194 Brit. J. of Psych. 355, 357 (2009).
[52] MDMA Report, at 7 n.9 (citing https://www.erowid.org).

is a stimulant and a hallucinogen whereas cocaine is merely a stimulant[53] — assuming that harm to humans can be gauged by summing the number of properties a drug has rather than measuring its actual effects. As experts for both the defense and the government agreed at the New York hearing, simply counting the number of properties a drug exhibits does not provide any information on its harmfulness.[54]

C. Recent Studies Reveal That The Commission's Report Overstated The Actual Harms of MDMA.

Research since 2001 refutes the Commission's conclusions regarding the harms of MDMA. The Commission attributed a variety of harms to MDMA, including memory impairment, increases in heart rate and body temperature, and even death.[55] In the years since the Commission's 2001 Report, memory effects among MDMA users have been shown to be negligible or moderate, with users testing well within normal limits.[56] Experts for both the defense and the government at the New York hearing acknowledged a particular 2009 meta-analysis by Rogers and colleagues as a helpful synthesis of MDMA study data;[57] according to this meta-analysis, which synthesized the results of hundreds of MDMA studies, the effects of MDMA on memory, though statistically significant, were nonetheless "small," with the mean scores of users falling within normal ranges.[58] Even one of the government's experts accepted the conclusions of Rogers and others that MDMA users' neurocognitive functioning, though impaired, nonetheless

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[53] *Id.* at 5.
[54] *See* Ex. 1, N.Y. Hrg. Tr. at 98-99 (Curran, defense expert); *id.* at 387 (Hanson, government expert).
[55] MDMA Report, at 7, 9.
[56] *See, e.g.,* Jager et al., *Incidental Use of Ecstasy: No Evidence for Harmful Effects on Cognitive Brain Function in a Prospective fMRI Study*, 193(3) Psychopharmacology (Berl.) 403, 403 (2007).
[57] *See* Ex. 1, N.Y. Hrg. Tr. at 18-19 (Curran, defense expert); *id.* at 239, 263 (Parrott, government expert).
[58] Rogers et al., *The harmful health effects of recreational ecstasy: a systematic review of observational evidence, Health Tech. Assessment*, Jan. 2009, at *xi*.

remained "[w]ithin the normal range."[59] The heart rate and temperature increases associated with MDMA use are minor (unlike the cardiovascular effects of cocaine) and are usually no greater than the increases associated with moderate exercise.[60] Controlled administration of MDMA to human subjects in studies examining the therapeutic effects of MDMA have resulted in no serious adverse reactions among study participants.[61] The most significant effects of MDMA are limited to the immediate rise in heart rate and body temperature, and a short-term change in brain chemistry, but even the government's experts acknowledged that all of these effects generally wear off within a week.[62] As the 2009 Rogers meta-analysis summarizes, what deficits do exist among MDMA users are "unlikely" to "significantly impair the average ecstasy user's everyday functional or quality of life."[63] Finally, deaths from MDMA are quite rare: one British study examining deaths over a ten-year period found approximately 10 deaths per year attributable to MDMA use alone;[64] this represents, on average, approximately 2 deaths per 100,000 MDMA users from 2001-07, or two thousandths of 1%.[65] At the New York

[59] Ex. 1, N.Y. Hrg. Tr. at 264 (Parrott, government expert).
[60] Jerome, *(+/-)-3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") Investigator's Brochure* 12 (2007).
[61] *Id.* at 17-20.
[62] *See* Ex. 1, N.Y. Hrg. Tr. at 243-44, 252 (Parrott, government expert); *id.* at 354 (Hanson, government expert).
[63] Rogers et al., *The harmful health effects of recreational ecstasy: a systematic review of observational evidence*, Health Tech. Assessment, Jan. 2009, at *xii*.
[64] *See* Schifano et al., *Overview of Amphetamine-Type Stimulant Mortality Data — UK, 1997-2007*, 61 Neuropsychobiology 122, 125 tbl. 1 (2010). This table, which covers mortality data for a ten-year period, found 104 "deaths where MDMA was identified on its own" as the cause of death. *Id.* This category is to be distinguished from the number at the top of the table, 605 deaths, which includes all individuals who had MDMA in their systems at the time of death. *Compare id.* at 123 (explaining that the greater figure, "np-SAD" deaths, includes cases in which coroners found the "presence of controlled drugs at post-mortem"), *with id.* at 124 (noting there were 104 cases out of the 605 in which ecstasy was "identified on its own" as the cause of death); *see also* Ex. 1, N.Y. Hrg. Tr. at 87 (Curran, defense expert) (explaining this distinction).
[65] *See* Schifano, 61 Neuropsychobiology at 128 tbl. 6; *see also* Rogers et al., *The harmful health effects of recreational ecstasy: a systematic review of observational evidence*, Health Tech. Assessment, Jan. 2009, at *xii* ("Ecstasy . . . remains a rare cause of death when reported as the sole drug associated with death related to drug use.").

hearing, experts for both the defense and the government noted that cocaine was a more frequent cause of death than MDMA,[66] and that death from MDMA is rare.[67]

As for the Commission's concerns about the hallucinogenic properties of MDMA, experts for both the defense and the government at the New York hearing cast doubt on the notion that MDMA could even be properly classified as a hallucinogen at all.[68] Thus the Commission seems to have in some sense misunderstood the very nature of the drug.

The Commission's inaccurate conclusions about the harms of MDMA at the time it devised the MDMA Guideline should not now form the basis for severe sentences for MDMA offenders.

D. The Commission's Non-Scientific Justification For The MDMA Guideline — The Fear Of Particular Harm To Youth — Has Not Been Borne Out By National Experience.

Although the Commission's principal findings concerned the harmfulness of MDMA, both in and of itself and relative to cocaine, the Commission's major non-scientific conclusion warrants brief discussion. Specifically, the Commission listed among its justifications for the current MDMA Guideline the fact that MDMA was heavily marketed to youth and that use began at an early age.[69] In this regard, as others, the Commission compared MDMA unfavorably to cocaine: indeed, one of the Commission's reasons for concluding that MDMA is more harmful than cocaine was that "powder cocaine is not as aggressively marketed to youth in the same manner as

[66] *See* Ex. 1, N.Y. Hrg. Tr. at 11 (Curran, defense expert); *id.* at 366 (Hanson, defense expert).
[67] *See* id. at 11 (Curran, defense expert); *id.* at 293 (Parrott, defense expert).
[68] *See* id. at 164 (Halpern, defense expert); id. at 289-90 (Parrott, government expert).
[69] MDMA Report, at 5, 12-14.

MDMA."[70] But the Commission's concern about youth use and youth harm has proved unfounded and the comparison to cocaine inapt.

According to the federally-funded "Monitoring the Future" survey by the University of Michigan, the percentage of 12th graders who use MDMA fell by more than half from 2001 to 2009.[71] At the New York hearing, a government expert who had been the head of the National Institute on Drug Abuse embraced this data, hypothesizing that young people became less open to trying MDMA because of their perception of its risk (as opposed to, for instance, the federal penal structure).[72] Thus the Commission's concerns over an impending MDMA epidemic among youth have not been realized.

Additionally, the national experience with MDMA has shown that MDMA does not pose a greater threat to the nation's youth than cocaine does. For example, in 2007 the number of cocaine-related emergency room visits was over four times the number of MDMA-related visits for youths aged twelve to seventeen, and for 18- to 20-year-olds, the number of cocaine-related visits was almost *nine* times the number than MDMA-related visits[73] — even though the overall usage rate for cocaine among each population was less than twice that of MDMA.[74]

In sum, it is clear that, in formulating the current MDMA Guideline, the Commission seriously overestimated the harmfulness of MDMA at a time when little was known about the substance. Because the MDMA Guideline is not based on sound

[70] *Id.* at 5.
[71] *See* Univ. of Mich., *Monitoring the Future: A Continuing Study of American Youth* (2009), tbl. 2 at 2 ("Trends in Annual Prevalence of Use of Various Drugs in Grades 8, 10, and 12"), *available at* http://monitoringthefuture.org/data/09data/pr09t2.pdf.
[72] Ex. 1, N.Y. Hrg. Tr. at 382 (Hanson, government expert).
[73] *See* DAWN 2007, at 25.
[74] See Ex. 2, NSDUH, tbls. 1.2A, 1.3A, 1.4A & 1.5A.

empirical evidence, but is instead the product of unsubstantiated fears and flawed research, the sentences recommended by the MDMA Guideline do not approximate sentences that are tailored to achieve the sentencing objectives in 18 U.S.C. § 3553(a). National experience and scientific research in the intervening decade demonstrate that MDMA is less harmful than the Commission and Congress had predicted, and that the current MDMA Guideline sentencing ranges are unduly severe. This Court should therefore exercise its discretion under *Kimbrough v. United States*, 552 U.S. 85 (2007), to vary from the scientifically-flawed and therefore unnecessarily harsh MDMA Guideline.

III. THIS COURT SHOULD SELECT A SENTENCE BASED ON THE ACTUAL HARMFULNESS OF MDMA RELATIVE TO OTHER DRUGS.

As previously noted, the 2001 amendments to the MDMA Guideline increased MDMA sentences by raising the ratio at which MDMA is converted to marijuana for sentencing purposes from 35:1 to a staggering 500:1.[75] Since this ratio is unreasonably high and devoid of an empirical basis, this Court must use its judgment to select the proper ratio.

Two useful comparators for MDMA are the drugs marijuana and ketamine. Like MDMA, both marijuana and ketamine appear in both the Drug Equivalency Tables, were evaluated in the three above-cited studies comparing the relative harms of various drugs based on expert assessments,[76] and were the subject of expert testimony and comparative evaluation at the New York hearing. A comparison of MDMA with these two drugs suggests that this Court should treat 1 gram of MDMA as equivalent to 1 gram of

[75] *See* MDMA Report, at 5-6; U.S.S.G. § 2D1.1, app. note 10(E), at 542 (2009).
[76] *See supra* Part II.A.ii.

marijuana (which is treated the same as 1 gram of ketamine) for the purpose of sentencing. MDMA is no more harmful, and in some ways is substantially less harmful, than marijuana and ketamine, each of which is treated as equivalent to marijuana for the purpose of sentencing.

Marijuana and ketamine both appear in the Drug Equivalency Tables in U.S.S.G. 2D1.1. They are treated the same for federal sentencing purposes.[77] In the two *Lancet* studies comparing the relative harmfulness of twenty drugs, based on experts' assessments of each drug's harmfulness to the individual user and to society, MDMA was ranked as seventeenth or eighteenth out of twenty — less harmful than ketamine (sixth or eighth) or marijuana (eleventh in both studies).[78] The Dutch comparative study likewise ranked MDMA (fourteenth) less harmful than ketamine (thirteenth) and marijuana (twelfth).[79]

The experts' decision to rank MDMA as less harmful than these two other drugs is well-founded. A brief comparison of each drug with MDMA bears out the conclusion that MDMA is no more harmful (and in many ways less harmful) than ketamine or marijuana. Studies have shown that unlike MDMA, a single dose of ketamine can produce schizophrenia-like symptoms, dissociative effects, and broad ranging cognitive dysfunction.[80] Also in stark contrast to MDMA, ketamine use has been shown to cause

[77] U.S.S.G. § 2D1.1, app. note 10(E), at 543.
[78] *See* Nutt 2007, 369 The Lancet at 1049-50; Nutt 2010, 376 The Lancet at 1561.
[79] *See* van Amsterdam, 16 Eur. Addiction Research at 204.
[80] *See* Morgan et al., *Consequences of Chronic Ketamine Self-Administration Upon Neurocognitive Function and Psychological Wellbeing: A 1-year Longitudinal Study*, 105 Soc. for the Study of Addiction 121, 121 (2009).

destruction of the lower urinary tract, including ulcerative cystitis and blood in urine.[81] Smoking marijuana increases health risks associated with smoking cigarettes, including coughing, chronic bronchitis, shortness of breath, and lung damage.[82] Citing many of these same harms, plus the greater potential for addictiveness of marijuana in contrast to MDMA, a defense expert who has worked with and published on all three substances — MDMA, ketamine, and marijuana — gave unchallenged and unrefuted testimony at the New York hearing that MDMA was no more harmful than ketamine or marijuana.[83]

Since MDMA is no more harmful (and in many respects less harmful) than ketamine or marijuana, MDMA should not be sentenced more harshly than either of these drugs. Therefore, this Court should treat 1 gram of MDMA as equivalent to 1 gram of marijuana (or 1 gram of ketamine, which the Guidelines treat as 1:1 with marijuana).

In the alternative, this Court should at the very least wipe out the effect of the 2001 amendments and their crumbling scientific foundation by returning to the pre-2001 ratio of 35:1 for converting MDMA to marijuana.[84]

IV. GUIDELINE CALCULATIONS

Mr. Phan has pled guilty to conspiracy to distribute 160,000 pills of MDMA. Mr. Phan submits that this Court should, after calculating the Guideline sentence, express a policy disagreement with the MDMA Guideline and impose a sentence based on a 1:1 rather than a 500:1 conversion ratio to marijuana. The PSR uses a weight of 52 kg as the

[81] *See* Shahani et al., *Ketamine-Associated Ulcerative Cystitis: A New Clinical Entity*, 69(5) Urology 810, 811 (2007).
[82] *See* U.S. Drug Enforcement Admin., *The DEA Position on Marijuana* (May 2006).
[83] *See* Ex. 1, N.Y. Hrg. Tr. at 7-8, 41-46 (Curran, defense expert).
[84] *See* MDMA Report, at 5-6.

corresponding weight of 160,000 pills. Under U.S.S.G. § 2D1.1(c)(10), the base offense level for 52 kg of marijuana is 20. (In the alternative, if this Court expresses a policy disagreement with the Guidelines but uses the 35:1 MDMA-to-marijuana conversion ratio that governed prior to the flawed 2001 MDMA Guideline, the resulting base offense level for 52 kg of MDMA would be that for 1,820 kg of marijuana, which is level 32. *See* U.S.S.G. § 2D1.1(c)(4).

If the Court uses a marijuana-MDMA ratio of 1:1, the resulting level, starting at 20 and accounting for the adjustments advised in the PSR, is 22. Since Mr. Phan is in Criminal History Category I, the appropriate sentencing range would be 41 to 51 months.

If the Court uses a marijuana-MDMA ratio of 35:1, the resulting level, starting at 32 and accounting for the adjustments advised in the PSR, is 34. Since Mr. Phan is in Criminal History Category I, the appropriate sentencing range would be 151 to 188 months.

The Court should begin with one of the above ranges before making its "individualized assessment based on the facts presented" in light of the sentencing factors Congress has set forth in 18 U.S.C. § 3553(a). *Gall*, 552 U.S. at 49-50; *see also United States v. Lewis*, 623 F. Supp. 2d 42, 47 (D.D.C. 2009) (stating that categorical policy disagreements should be applied before individual considerations); *United States v. Beiermann*, 599 F. Supp. 2d 1087, 1107-08 (N.D. Iowa 2009) (applying categorical policy disagreement before adjusting for individual circumstances); *accord*, *United States v. Greer*, 699 F. Supp. 2d 876, 880 (E.D. Tex. 2010); *United States v. Edwards*, 693 F. Supp. 2d 575, 582-84 (S.D. W. Va. 2010); *United States v. Williams*, No. 09-CR-30099,

2010 WL 1325229, at *8 (S.D. Ill. Mar. 30, 2010); *Henderson v. United States*, 660 F. Supp. 2d 751, 753-54 (E.D. La. 2009); *United States v. Dozier*, No. S1 08 Cr. 08-02, 2009 WL 1286486, at *6-7 (S.D.N.Y. May 8, 2009).

The application of the 3553(a) factors to Mr. Phan is addressed in the separate sentencing memorandum submitted by co-counsel from the Federal Public Defender.

CONCLUSION

Because the MDMA Guideline promulgated in 2001 and still on the books today was the product of fear and sloppy science rather than empirically sound study, this Court has discretion to vary from the prescribed Guideline offense levels and should do so — either at this time, or if the Court would prefer, after an evidentiary hearing at which the Court may hear from scientific experts about the actual harmfulness of MDMA and the research that has undermined the Commission's 2001 conclusions.

Taking into account the actual harms of MDMA, in comparison to the ranges prescribed for marijuana and ketamine, this Court should begin with a sentencing range of 41 to 51 months before considering Mr. Phan's individual circumstances under 18 U.S.C. § 3553(a). Alternatively, if this Court wishes to do no more than reverse the effects of the flawed 2001 Guideline, it should begin with a sentencing range of 151-188 months. Either way, it is vital that this Court exercise its independent judgment to preserve fairness and ensure that the resulting sentence for Mr. Phan is "sufficient but not greater than necessary" to serve the goals of sentencing. 18 U.S.C. § 3553(a). Once this Court has identified a fair and realistic Guideline range, it should address Mr. Phan's

individualized circumstances as discussed in the sentencing memorandum from co-counsel and as required under § 3553(a).

DATED this 4th day of January, 2011.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on January 4, 2011, I electronically filed the foregoing with the Clerk of the Court using the CM/ECF system which will send notification of such filing to Assistant United States Attorney Susan M. Roe.

I further certify that I have emailed the above document to non CM/ECF participant United States Probation Officer Lisa L. Combs.

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APPENDIX C

US v. McCarthy (S.D. NY 2011), Memorandum and Order ("*McCarthy* order")

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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UNITED STATES OF AMERICA, :

-against- : 09 Cr. 1136 (WHP)

SEAN MCCARTHY, : MEMORANDUM & ORDER

Defendant. :

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WILLIAM H. PAULEY III, United States District Judge:

On February 19, 2010, Defendant Sean McCarthy pled guilty to conspiracy to distribute and possess with the intent to distribute 37,120 grams of MDMA, commonly known as "Ecstasy," in violation of 21 U.S.C. § 841. McCarthy argues that this Court should depart from the United States Sentencing Commission's (the "Commission") MDMA Sentencing Guidelines (the "Guidelines") asserting that the Commission's analysis was flawed and has been undermined by intervening scientific developments. On December 6 and 7, 2010, this Court held an evidentiary hearing on these issues.[1] For the following reasons, this Court finds that a 500:1 MDMA-to-marijuana equivalency would give rise to a sentence that is greater than necessary to serve the objectives of sentencing. Accordingly, this Court adopts a marijuana equivalency of 200 grams for MDMA.

BACKGROUND

Prior to 2001, the Guidelines held that one gram of MDMA was equivalent to 35 grams of marijuana. United States Sentencing Commission, Report to Congress: MDMA Drug

[1] This Court heard testimony from four expert witnesses: Drs. Helen Curran and John Halpern for the Defendant, and Drs. Andrew Parrott and Glen Hanson for the Government.

Offenses, Explanation of Recent Guideline Amendments ("Ecstasy Report") 6 (2001). In 2000, however, Congress passed the Ecstasy Anti-Proliferation Act, which directed the Commission to review and increase penalties for any offense relating to the manufacture and trafficking of MDMA, and required the Commission to submit a report on the resulting amendments to Congress. Pub. L. No. 106-310, 114 Stat. 1101, 1241-45.

The Ecstasy Report determined that penalties for MDMA offenses should be more severe than for powder cocaine, which has a 200:1 marijuana equivalency, but less severe than for heroin, which has a 1000:1 marijuana equivalency. Ecstasy Report 5. The Commission decided on less severe sentences for MDMA offenses than for heroin because:

> (1) there are many more heroin cases in the federal system than MDMA cases, (2) heroin is more addictive than MDMA, (3) heroin has many more emergency room visits and deaths associated with its use than MDMA because, unlike MDMA which generally is taken orally, heroin is injected, (4) heroin has more violence associated with both its users and distribution system than MDMA, in part because MDMA users typically do not resort to violence to support their drug use, and (5) heroin causes greater secondary health effects, such as the spread of HIV and hepatitis, because it is injected.

Ecstasy Report 5. The Commission offered three reasons for imposing higher sentences for MDMA offenses than for powder cocaine: "(1) unlike MDMA, powder cocaine is not neurotoxic, (2) powder cocaine is not aggressively marketed to youth in the same manner as MDMA, and (3) powder cocaine is only a stimulant, but MDMA acts as both a stimulant and a hallucinogen." Ecstasy Report 5. Ultimately, the Commission established an MDMA-to-marijuana equivalency of 500 grams. Ecstasy Report 5.

DISCUSSION

I. Applicable Law

The Sentencing Guidelines are "advisory." United States v. Booker, 543 U.S. 220, 244-45 (2005); see also United States v. Dorvee, 616 F.3d 174, 183 (2d Cir. 2010). Accordingly, "a district court may vary from the Guidelines range based solely on a policy disagreement with the Guidelines, even where that disagreement applies to a wide class of offenders or offenses." Dorvee, 550 F.3d at 191; see also Kimbrough v. United States, 552 U.S. 85, 91 (2007) (district court did not abuse its discretion in issuing a non-Guidelines sentence for a crack cocaine offense, based on lack of empirical basis for 100:1 sentencing disparity between crack cocaine and powder cocaine sentences). A court is free to determine that the "Guidelines are not based on empirical data and national experience, and hence 'do not exemplify the Commission's exercise of its characteristic institutional role.'" United States v. Cavera, 550 F.3d 180, 192 (2d Cir. 2008) (quoting Kimbrough, 552 U.S. at 109). This determination may be based on a finding that the Guidelines "rest[] on assumptions about . . . relative harmfulness . . . that more recent research and data no longer support." Kimbrough, 552 U.S. at 98.

II. Empirical Basis of MDMA Guidelines

A. Continuing Validity of the Commission's Findings

McCarthy challenges the MDMA Guidelines on the grounds that recent research undercuts the Commission's finding that MDMA is neurotoxic. The Ecstasy Report noted that a 1998 "brain scan comparison of MDMA users with non-users indicated the users had significantly reduced number of serotonin transporters throughout the brain." Ecstasy Report 9 (citing U.D. McCann et al., Positron Emission Tomographic Evidence of Toxic Effect of

MDMA ("Ecstasy") on Brain Serotonin Neurons in Human Beings (the "McCann Study"), 352 Lancet 1433 (1998)). Both parties' experts agreed that the best and most recent study of MDMA's effects on serotonin transporters found a reduction in serotonin transporters, but only in the cerebral cortex and hippocampus. See S.J. Kisch et al., Decreased Cerebral Cortical Serotonin Transporter Binding in Ecstasy Users: A Positron Emission Tomography/[(11)C] DASB and Structural Brain Imaging Study (the "Kisch Study"), 133 Brain 1779 (2010). Importantly, the Kisch Study expressly noted that it "did not find a global, massive reduction of brain [serotonin transporter] binding as reported in the [McCann study]." Kisch at 1791; (see also Tr. 257-58 (Parrott) (discussing the differences between the McCann and Kisch studies).)

While both parties rely on the Kisch Study, its import is equivocal: the Kisch Study found less depletion in serotonin transporters than the McCann Study, but nevertheless confirmed that depletion occurs. The variation in findings between the two studies may be explained by differences in the level of MDMA use among the test subjects. (Tr. 257-58 (Parrott).) Recent studies on the effect of MDMA on cognitive functioning have also found that MDMA use can cause statistically significant (although relatively minor) impairment in memory, providing further support for the Commission's findings. (See Tr. 197 (Parrott), 263 (Parrott).) Moreover, while early MDMA studies have been criticized because they failed to consider confounding variables like polydrug use (Tr. 119 (Halpern)), the Kisch Study took those variables into account (Tr. 180 (Parrott)). And in any case, the overwhelming majority of MDMA users are polydrug users. (Tr. 331 (Hanson).) Thus, the effects of MDMA in conjunction with other drugs remains a highly relevant—and arguably more practical—consideration when determining the harm caused by MDMA. (Tr. 331-32 (Hanson).)

Accordingly, this Court cannot conclude that the Commission's findings on MDMA's neurotoxicity have been so compromised by subsequent research that they are no longer true.

Nor can this Court discount the Commission's finding that MDMA is uniquely marketed to—and prevalent within—the younger population. Prevalence of a drug among the nation's youth, a particularly vulnerable segment of the population, provides strong support for higher sentences. This Court was not presented with any evidence contradicting this finding. Although McCarthy correctly notes that MDMA use has declined since its apex in the late 1990s and early 2000s, it is again on the rise. See National Institute of Health, Monitoring the Future: National Results on Adolescent Drug Use, Overview of Key Findings 46 (2008).

However, the Commission's statement that cocaine is only a stimulant, while MDMA is both a stimulant and a hallucinogen, is without factual support and largely irrelevant. Experts for both parties testified that MDMA is not properly characterized as a "hallucinogen." (Tr. 98 (Curran), 149 (Halpern), 289-90 (Parrott).) And in any case, comparing pharmacological properties using broad descriptors like "stimulant" and "hallucinogen" says little—if anything—about the relative harm posed by a drug. (See Tr. 128-29 (Halpern) ("[The Ecstasy Report] almost read[s] like this was supposed to be some sort of arithmetic; cocaine gets a score of one [because] it's a stimulant and then MDMA gets a score of two because it's a stimulant and a hallucinogen. . . . [T]hat's not using good science."))

B. Strength of the Commission's Analysis

There is no question that MDMA use has several significant negative impacts. Yet the Commission's analysis of these impacts—particularly as compared to cocaine—was selective and incomplete. Rather than comparing the full range of health effects of MDMA and cocaine, for example, the Commission focused only on a single health effect: neurotoxicity. In

doing so, the Commission ignored several effects of cocaine that render it significantly more harmful than MDMA.

For example, cocaine is responsible for far more emergency room visits per year than MDMA. (See Def.'s Third Supp. Sentencing Mem. Ex. 2: U.S. Department of Health and Human Services, Drug Abuse Warning Network 2007: National Estimates of Drug-Related Emergency Department Visits ("DAWN") 22 (2010) (finding that cocaine abuse was responsible for 553,530 emergency room visits, or 29.4% of drug- or alcohol-related emergency room visits in 2007, while MDMA was responsible for 12,748 visits, or 0.7%); (see also Tr. 125-26 (Halpern), 373-74 (Hanson).) Even controlling for the fact that cocaine is more commonly used than MDMA, cocaine is still approximately 16 times more likely to lead to hospitalization. (Compare DAWN 22, with Def.'s Third Supp. Sentencing Mem. Ex. 3: U.S. Department of Health and Human Services, Results from the 2007 National Survey on Drug Use and Health 252 (2008) (finding that 5,738,000 people over the age of 12 used cocaine in 2007, while 2,132,000 people used MDMA); (see also Tr. 126 (Halpern).) As the Government's witnesses acknowledged, MDMA fatalities are "rare." (Tr. 293 (Parrott); see also Tr. 374 (Hanson).)

Cocaine is also far more addictive than MDMA. (Tr. 230 (Parrott), 291 (Parrott), 339 (Hanson).) Indeed, MDMA is "one of the least addictive drugs." (Tr. 212 (Parrott), 232 (Parrott).) Moreover, cocaine use causes several adverse health effects not implicated by MDMA use—such as "cardiovascular effects, including disturbances in heart rhythm and heart attacks; respiratory effects, such as chest pain and respiratory failure; [and] neurological effects, including strokes [and] seizures." United States Sentencing Commission, Report to Congress: Cocaine and Federal Sentencing Policy ("Cocaine Report") 65 (2007); (see also Tr. 128 (Halpern) ("[C]ocaine users after many years of abuse and heavy use, run the risk of heart attack,

of stroke, of death from that, and many other problems. . . . We can do a standard CAT scan of the brain that can show evidence of strokes in the brain from their repeated longstanding cocaine use.").) In addition, MDMA is not associated with significant secondary health effects such as, for example, the spread of HIV through needles. Ecstasy Report 19. In this regard, MDMA and cocaine are similar.

Moreover, in contrast to MDMA, cocaine trafficking is associated with substantial violence. Ecstasy Report 19; see also Cocaine Report 86. And finally, there are far more cocaine-related cases in the federal criminal justice system than MDMA-related cases. See U.S. Department of Justice, Bureau of Justice Statistics, 2008 Statistical Tables 9 (2008), available at http://bjs.ojp.usdoj.gov/content/pub/html/fjsst/2008/fjs08st.pdf.

The foregoing illustrates that the Commission's analysis focused on the few ways in which MDMA is more harmful than cocaine, while disregarding several significant factors suggesting that it is in fact less harmful. Such opportunistic rummaging is particularly stark when viewed against the Commission's rationale for adopting lighter sentences for MDMA than for heroin. In that context, the Commission found that five factors weighed in favor of lighter sentences for MDMA: (1) number of cases in the federal criminal justice system, (2) addiction potential, (3) emergency room visits, (4) violence associated with use and distribution, and (5) secondary health effects. As discussed above, these factors—with the exception of secondary health effects, which are similar for MDMA and cocaine—also weigh in favor of lower sentences for MDMA than for cocaine. Yet they appear to have played no role in the Commission's MDMA Guidelines determination. See Ecstasy Report 5. The Commission's selective analysis is incompatible with the goal of uniform sentencing based on empirical data.

This Court is mindful of the harm inflicted by drug abuse and trafficking. The distribution of illegal drugs is a serious crime warranting significant penalties. Yet this Court must also consider "the need to avoid unwarranted sentence disparities among defendants with similar records who have been found guilty of similar conduct." 18 U.S.C. § 3553. This fundamental principle is violated when disparate drug equivalencies are established for similar narcotics based on an incomplete analysis. See Kimbrough, 552 U.S. at 98. Ultimately, consistent with the overwhelming weight of the evidence, no witness testified that MDMA was more harmful than cocaine. (Tr. 40 (Curran), 44 (Curran), 127-28 (Halpern), 231-32 (Parrott), 343 (Hanson).)

McCarthy suggests that this Court should sentence him based on a ratio of 1:1 or, alternatively, on the pre-2001 ratio of 35:1. However, he has not presented sufficient evidence that the harm posed by MDMA is equal to that of marijuana. Nor does this Court believe that the record supports a ratio of 35:1. Although McCarthy points to several aspects in which MDMA is less harmful than cocaine, MDMA also presents its own unique dangers. This Court defers to the Commission's determination, supported by express Congressional findings, that the pre-2001 MDMA Guidelines were too low. Accordingly, this Court adopts an MDMA-to-marijuana equivalency of 200:1, equal to that of cocaine.[2] See Spears v. United States, 129 S. Ct. 840, 843 (2009) ("[T]he ability to reduce a mine-run defendant's sentence [under Kimbrough and Booker] necessarily permits adoption of a replacement ratio.").

[2] As noted, much of the evidence indicates that MDMA is less harmful than cocaine, suggesting that an even lower equivalency may be appropriate given a sufficient factual foundation in a later case.

CONCLUSION

For the foregoing reasons, this Court adopts an MDMA-to-marijuana equivalency of 200:1.

Dated: May 19, 2011
New York, New York

SO ORDERED:

WILLIAM H. PAULEY III
U.S.D.J.

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APPENDIX D

MAPS/ACLU Sentencing Press Release

FOR IMMEDIATE RELEASE
July 15, 2011

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MAPS Helps ACLU Persuade Federal Judge To Use Scientific Evidence to Challenge Harsh Ecstasy Sentencing Guidelines

Santa Cruz, CA – On July 15, 2011, U.S. District Judge William Pauley III sentenced a defendant charged with selling Ecstasy to 26 months in prison, less than half the 63 to 78 months recommended by current sentencing guidelines. This watershed event took place because the American Civil Liberties Union (ACLU), which represented the defendant, presented scientific evidence challenging the sentencing guidelines as being promulgated in a time of irrational fear over the risks of MDMA, based on claims made at the time that are unsupported by current scientific evidence.*

Previously, on May 19, 2011, Judge Pauley ruled that Ecstasy-related crimes are punished far more harshly than is justified by currently available scientific evidence about the risks of the drug. This ruling is the first of its kind regarding Ecstasy, yet it mirrors similar judicial rulings that have successfully challenged the sentencing guidelines for crack cocaine as also being too harsh and unsupported by current scientific evidence.

In 2001, the US Sentencing Commission enacted a set of guidelines requiring judges to treat a single gram of Ecstasy as if it were 500 grams of marijuana for the purposes of determining the severity of a sentence for federal drug offenses involving Ecstasy. At the public hearing prior to the Sentencing Commission's determination of the Ecstasy sentencing guidelines, MAPS Executive Director Rick Doblin, Ph.D., and other experts presented testimony, but that testimony was ignored. The ACLU challenged the Sentencing Commission's standard as unfair and requested that the judge undertake a rational reconsideration of the guidelines.

Judge Pauley's ruling sharply criticizes the commission's "opportunistic rummaging" and "selective and incomplete" analysis of the scientific data that led to the creation of the guidelines, and took into account new evidence—including data from a recent National Institute on Drug Abuse (NIDA)-funded study by Harvard psychiatrist John Halpern, M.D.—showing that long-term recreational Ecstasy use did not cause clinically significant cognitive damage.

MAPS brought the idea for the Ecstasy neurocognitive study idea to Dr. Halpern and invested $15,000 in a pilot study. Dr. Halpern then used the data from the pilot study for his successful NIDA grant application for which he was awarded $1.8 million over five years. MAPS also consulted with ACLU lawyers on the case and shared its review of the entire scientific literature about Ecstasy and MDMA, including data from its international series of Phase 2 pilot studies into MDMA-assisted psychotherapy for subjects with chronic, treatment-resistant posttraumatic stress disorder (PTSD).

According to Scott Michelman, staff attorney for the ACLU Criminal Drug Law Reform Project, the ruling is a step in the right direction. He commented, "This ruling demonstrates the importance of thoroughly reviewing the empirical basis underlying each of the U.S. Sentencing Guidelines for drug offenses, to make sure the Guidelines reflect the current state of scientific knowledge."

***Note: MAPS' clinical research studies use pure MDMA manufactured in government-licensed facilities. Drugs bought and sold on the black market as "Ecstasy" may or may not contain MDMA.**

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APPENDIX E

Media Highlights

Multiple news sources have reported on MAPS MDMA research. A brief list of media from the past year include:

- **The New York Times**: F.D.A. Agrees to New Trials for MDMA as Relief for PTSD Patients (November 30, 2016)

- **PBS Newshour**: Using Ecstasy to Treat PTSD: 'I Felt Like My Soul Snapped Back into Place' (December 1, 2016)
- **Red State**: The Cure for PTSD? How a Rave Drug Can Be a Treatment (November 16, 2016)
- **Stars and Stripes**: Ecstasy One Step Closer to Approval as PTSD Treatment (December 20, 2016)
- **Fox News**: Ecstasy Trials Approved by FDA for PTSD Patients (November 30, 2016)
- **Military.com**: Trial for PTSD Treatment with Ecstasy Ingredient to Open Soon (January 26, 2017)
- **The Guardian**: 'My Therapist Gave Me a Pill': Can MDMA Help Cure Trauma? (September 16, 2016)

A more extensive list of MAPS media coverage is also available on our website at maps.org/news/media