

244. Pacifici, R., et al., *Immunomodulating properties of MDMA alone and in combination with alcohol: a pilot study*. Life Sci, 1999. **65**(26): p. L309-16.
245. Pacifici, R., et al., *Acute effects of 3,4-methylenedioxymethamphetamine alone and in combination with ethanol on the immune system in humans*. J Pharmacol Exp Ther, 2001. **296**(1): p. 207-15.
246. Pacifici, R., et al., *Effects of repeated doses of MDMA ("ecstasy") on cell-mediated immune response in humans*. Life Sci, 2001. **69**(24): p. 2931-41.
247. Pacifici, R., et al., *Combined immunomodulating properties of 3,4-methylenedioxymethamphetamine (MDMA) and cannabis in humans*. Addiction, 2007. **102**(6): p. 931-6.
248. Randall, S., et al., *Effects of acute 3,4-methylenedioxymethamphetamine on sleep and daytime sleepiness in MDMA users: a preliminary study*. Sleep, 2009. **32**(11): p. 1513-9.
249. Carhart-Harris, R.L., et al., *Equivalent effects of acute tryptophan depletion on REM sleep in ecstasy users and controls*. Psychopharmacology (Berl), 2009. **206**(2): p. 187-96.
250. Allen, R.P., U.D. McCann, and G.A. Ricaurte, *Persistent effects of (+/-)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on human sleep*. Sleep, 1993. **16**(6): p. 560-4.
251. McCann, U.D., S.C. Peterson, and G.A. Ricaurte, *The effect of catecholamine depletion by alpha-methyl-para-tyrosine on measures of cognitive performance and sleep in abstinent MDMA users*. Neuropsychopharmacology, 2007. **32**(8): p. 1695-706.
252. McCann, U.D., et al., *Sleep deprivation differentially impairs cognitive performance in abstinent methylenedioxymethamphetamine ("ecstasy") users*. J Neurosci, 2009. **29**(44): p. 14050-6.
253. McCann, U.D., et al., *Sleep apnea in young abstinent recreational MDMA ("ecstasy") consumers*. Neurology, 2009. **73**(23): p. 2011-7.
254. McElhatton, P.R., et al., *Congenital anomalies after prenatal ecstasy exposure [letter]*. Lancet, 1999. **354**(9188): p. 1441-2.
255. Bateman, D.N., et al., *A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England*. Eur J Clin Pharmacol, 2004. **60**(9): p. 635-41.
256. Ho, E., L. Karimi-Tabesh, and G. Koren, *Characteristics of pregnant women who use Ecstasy (3, 4- methylenedioxymethamphetamine)*. Neurotoxicol Teratol, 2001. **23**(6): p. 561-7.
257. Singer, L.T., et al., *Neurobehavioral outcomes of infants exposed to MDMA (Ecstasy) and other recreational drugs during pregnancy*. Neurotoxicol Teratol, 2012. **34**(3): p. 303-10.
258. von Sydow, K., et al., *Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults-a transient phenomenon? Results from a longitudinal community study*. Drug Alcohol Depend, 2002. **66**(2): p. 147-59.
259. Cottler, L.B., et al., *Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria*. Hum Psychopharmacol, 2001. **16**(8): p. 599-606.
260. Topp, L., et al., *Ecstasy use in Australia: patterns of use and associated harm*. Drug Alcohol Depend, 1999. **55**(1-2): p. 105-15.
261. Dumont, G.J. and R.J. Verkes, *A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers*. J Psychopharmacol, 2006. **20**(2): p. 176-87.

262. Lamers, C.T., et al., *Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance*. J Psychopharmacol, 2003. **17**(4): p. 379-87.
263. Tancer, M.E. and C.E. Johanson, *The subjective effects of MDMA and mCPP in moderate MDMA users*. Drug Alcohol Depend, 2001. **65**(1): p. 97-101.
264. Huxster, J.K., A. Pirona, and M.J. Morgan, *The sub-acute effects of recreational ecstasy (MDMA) use: a controlled study in humans*. J Psychopharmacol, 2006. **20**(2): p. 281-90.
265. Pirona, A. and M.J. Morgan, *An investigation of the subacute effects of ecstasy on neuropsychological performance, sleep and mood in regular ecstasy users*. J Psychopharmacol, 2010. **24**(2): p. 175-85.
266. Mithoefer, M.C., et al., *The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study*. J Psychopharmacol, 2010.
267. Hoshi, R., J. Bisla, and H.V. Curran, *The acute and sub-acute effects of 'ecstasy' (MDMA) on processing of facial expressions: preliminary findings*. Drug Alcohol Depend, 2004. **76**(3): p. 297-304.
268. Bosker, W.M., et al., *Dose-related effects of MDMA on psychomotor function and mood before, during, and after a night of sleep loss*. Psychopharmacology (Berl), 2010. **209**(1): p. 69-76.
269. Gamma, A., et al., *3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H(2)(15)O]-PET in healthy humans*. Neuropsychopharmacology, 2000. **23**(4): p. 388-95.
270. Phelps, E.A., et al., *Activation of the left amygdala to a cognitive representation of fear*. Nat Neurosci, 2001. **4**(4): p. 437-41.
271. Cohen, R.S., *Subjective reports on the effects of the MDMA ('ecstasy') experience in humans*. Prog Neuropsychopharmacol Biol Psychiatry, 1995. **19**(7): p. 1137-45.
272. McGuire, P.K., H. Cope, and T.A. Fahy, *Diversity of psychopathology associated with use of 3,4-methylenedioxymethamphetamine ('Ecstasy')*. Br J Psychiatry, 1994. **165**(3): p. 391-5.
273. Huizink, A.C., et al., *Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study*. Bmj, 2006. **332**(7545): p. 825-8.
274. Williams, H., et al., *"Saturday night fever": ecstasy related problems in a London accident and emergency department*. J Accid Emerg Med, 1998. **15**(5): p. 322-6.
275. MacInnes, N., S.L. Handley, and G.F. Harding, *Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms*. J Psychopharmacol, 2001. **15**(3): p. 181-6.
276. Parrott, A.C., E. Sisk, and J.J. Turner, *Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users*. Drug Alcohol Depend, 2000. **60**(1): p. 105-10.
277. Sumnall, H.R. and J.C. Cole, *Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis*. J Psychopharmacol, 2005. **19**(1): p. 84-92.
278. Milani, R.M., et al., *Gender differences in self-reported anxiety, depression, and somatization among ecstasy/MDMA polydrug users, alcohol/tobacco users, and nondrug users*. Addict Behav, 2004. **29**(5): p. 965-71.
279. Sumnall, H.R., G.F. Wagstaff, and J.C. Cole, *Self-reported psychopathology in polydrug users*. J Psychopharmacol, 2004. **18**(1): p. 75-82.

280. Medina, K.L. and P.K. Shear, *Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: contributions of polydrug use*. *Drug Alcohol Depend*, 2007. **87**(2-3): p. 303-11.
281. Fisk, J.E., et al., *Modelling the adverse effects associated with ecstasy use*. *Addiction*, 2011. **106**(4): p. 798-805.
282. Scott, L.A., et al., *The impact of comorbid cannabis and methamphetamine use on mental health among regular ecstasy users*. *Addict Behav*, 2012. **37**(9): p. 1058-62.
283. Kuypers, K.P. and J.G. Ramaekers, *Transient memory impairment after acute dose of 75mg 3,4-Methylene-dioxymethamphetamine*. *J Psychopharmacol*, 2005. **19**(6): p. 633-9.
284. Ramaekers, J.G. and K.P. Kuypers, *Acute effects of 3,4-methylenedioxyamphetamine (MDMA) on behavioral measures of impulsivity: alone and in combination with alcohol*. *Neuropsychopharmacology*, 2006. **31**(5): p. 1048-55.
285. Kuypers, K.P., N. Samyn, and J.G. Ramaekers, *MDMA and alcohol effects, combined and alone, on objective and subjective measures of actual driving performance and psychomotor function*. *Psychopharmacology (Berl)*, 2006. **187**(4): p. 467-75.
286. Kuypers, K.P. and J.G. Ramaekers, *Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected*. *Psychopharmacology (Berl)*, 2007. **189**(4): p. 557-63.
287. Ramaekers, J.G., K.P. Kuypers, and N. Samyn, *Stimulant effects of 3,4-methylenedioxyamphetamine (MDMA) 75 mg and methylphenidate 20 mg on actual driving during intoxication and withdrawal*. *Addiction*, 2006. **101**(11): p. 1614-21.
288. Laws, K.R. and J. Kokkalis, *Ecstasy (MDMA) and memory function: a meta-analytic update*. *Hum Psychopharmacol*, 2007.
289. Zakzanis, K.K., Z. Campbell, and D. Jovanovski, *The neuropsychology of ecstasy (MDMA) use: a quantitative review*. *Hum Psychopharmacol*, 2007. **22**(7): p. 427-35.
290. Murphy, P.N., et al., *The effects of 'ecstasy' (MDMA) on visuospatial memory performance: findings from a systematic review with meta-analyses*. *Hum Psychopharmacol*, 2012. **27**(2): p. 113-38.
291. Schilt, T., et al., *Long-term neuropsychological effects of ecstasy in middle-aged ecstasy/polydrug users*. *Psychopharmacology (Berl)*, 2010. **207**(4): p. 583-91.
292. Schilt, T., et al., *Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study*. *Arch Gen Psychiatry*, 2007. **64**(6): p. 728-36.
293. Jager, G., et al., *Incidental use of ecstasy: no evidence for harmful effects on cognitive brain function in a prospective fMRI study*. *Psychopharmacology (Berl)*, 2007. **193**(3): p. 403-14.
294. Halpern, J.H., et al., *Residual neuropsychological effects of illicit 3,4-methylenedioxyamphetamine (MDMA) in individuals with minimal exposure to other drugs*. *Drug Alcohol Depend*, 2004. **75**(2): p. 135-47.
295. Wareing, M., et al., *Verbal working memory deficits in current and previous users of MDMA*. *Hum Psychopharmacol*, 2004. **19**(4): p. 225-34.
296. Thomasius, R., et al., *Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users*. *Psychopharmacology (Berl)*, 2003. **167**(1): p. 85-96.
297. von Geusau, N.A., et al., *Impaired executive function in male MDMA ("ecstasy") users*. *Psychopharmacology (Berl)*, 2004. **175**(3): p. 331-41.
298. Murphy, P.N., et al., *Executive working memory deficits in abstinent ecstasy/MDMA users: a critical review*. *Neuropsychobiology*, 2009. **60**(3-4): p. 159-75.
299. Hoshi, R., et al., *Neurocognitive function in current and ex-users of ecstasy in*

- comparison to both matched polydrug-using controls and drug-naive controls.*  
Psychopharmacology (Berl), 2007. **194**(3): p. 371-9.
300. Roiser, J.P., et al., *The effect of polymorphism at the serotonin transporter gene on decision-making, memory and executive function in ecstasy users and controls.* Psychopharmacology (Berl), 2006. **188**(2): p. 213-27.
301. Cuyas, E., et al., *The Influence of Genetic and Environmental Factors among MDMA Users in Cognitive Performance.* PLoS One, 2011. **6**(11): p. e27206.
302. Schilt, T., et al., *The effect of Ecstasy on memory is moderated by a functional polymorphism in the catechol-O-methyltransferase (COMT) gene.* Eur Neuropsychopharmacol, 2009. **19**(2): p. 116-24.
303. Morgan, M.J., *Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity.* Neuropsychopharmacology, 1998. **19**(4): p. 252-64.
304. Quednow, B.B., et al., *Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy").* Psychopharmacology (Berl), 2007. **189**(4): p. 517-30.
305. Morgan, M.J., et al., *Elevated impulsivity and impaired decision-making in abstinent Ecstasy (MDMA) users compared to polydrug and drug-naive controls.* Neuropsychopharmacology, 2006. **31**(7): p. 1562-73.
306. Roiser, J.P., R.D. Rogers, and B.J. Sahakian, *Neuropsychological function in ecstasy users: a study controlling for polydrug use.* Psychopharmacology (Berl), 2007. **189**(4): p. 505-16.
307. Schilt, T., et al., *Decision making as a predictor of first ecstasy use: a prospective study.* Psychopharmacology (Berl), 2009. **203**(3): p. 519-27.
308. Hanson, K.L., M. Luciana, and K. Sullwold, *Reward-related decision-making deficits and elevated impulsivity among MDMA and other drug users.* Drug Alcohol Depend, 2008. **96**(1-2): p. 99-110.
309. Bedi, G. and J. Redman, *Metamemory in recreational ecstasy polydrug users: what do self-reports of memory failures mean?* J Psychopharmacol, 2008.
310. Bedi, G. and J. Redman, *Ecstasy use and higher-level cognitive functions: weak effects of ecstasy after control for potential confounds.* Psychol Med, 2008. **38**(9): p. 1319-30.
311. Hanson, K.L. and M. Luciana, *Neurocognitive impairments in MDMA and other drug users: MDMA alone may not be a cognitive risk factor.* J Clin Exp Neuropsychol, 2010. **32**(4): p. 337-49.
312. Halpern, J.H., et al., *Residual neurocognitive features of long-term ecstasy users with minimal exposure to other drugs.* Addiction, 2011. **106**(4): p. 777-86.
313. Raj, V., et al., *MDMA (ecstasy) use is associated with reduced BOLD signal change during semantic recognition in abstinent human polydrug users: a preliminary fMRI study.* J Psychopharmacol, 2010. **24**(2): p. 187-201.
314. Blagrove, M., et al., *Procedural and declarative memory task performance, and the memory consolidation function of sleep, in recent and abstinent ecstasy/MDMA users.* J Psychopharmacol, 2011. **25**(4): p. 465-77.
315. Kish, S.J., et al., *Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[<sup>11</sup>C]DASB and structural brain imaging study.* Brain, 2010. **133**(Pt 6): p. 1779-97.
316. Montgomery, C. and J.E. Fisk, *Ecstasy-related deficits in the updating component of executive processes.* Hum Psychopharmacol, 2008.
317. Hadjiefthyvoulou, F., et al., *Everyday and prospective memory deficits in ecstasy/polydrug users.* J Psychopharmacol, 2011. **25**(4): p. 453-64.

318. van Holst, R.J. and T. Schilt, *Drug-related decrease in neuropsychological functions of abstinent drug users*. *Curr Drug Abuse Rev*, 2011. **4**(1): p. 42-56.
319. Jager, G., et al., *Assessment of cognitive brain function in ecstasy users and contributions of other drugs of abuse: results from an fMRI study*. *Neuropsychopharmacology*, 2008. **33**(2): p. 247-58.
320. Indlekofer, F., et al., *Reduced memory and attention performance in a population-based sample of young adults with a moderate lifetime use of cannabis, ecstasy and alcohol*. *J Psychopharmacol*, 2009. **23**(5): p. 495-509.
321. Ramaekers, J.G., et al., *Involvement of Inferior Parietal Lobules in Prospective Memory Impairment during Acute MDMA (Ecstasy) Intoxication: An Event-Related fMRI Study*. *Neuropsychopharmacology*, 2008.
322. Kuypers, K.P., et al., *MDMA intoxication and verbal memory performance: a placebo-controlled pharmac-MRI study*. *J Psychopharmacol*, 2011. **25**(8): p. 1053-61.
323. Chang, L., et al., *Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study*. *Psychiatry Res*, 2000. **98**(1): p. 15-28.
324. de Win, M.M., et al., *A Prospective Cohort Study on Sustained Effects of Low-Dose Ecstasy Use on the Brain in New Ecstasy Users*. *Neuropsychopharmacology*, 2007. **32**(2): p. 458-470.
325. Frei, E., et al., *Localization of MDMA-induced brain activity in healthy volunteers using low resolution brain electromagnetic tomography (LORETA)*. *Hum Brain Mapp*, 2001. **14**(3): p. 152-65.
326. Bauernfeind, A.L., et al., *Human ecstasy use is associated with increased cortical excitability: an fMRI study*. *Neuropsychopharmacology*, 2011. **36**(6): p. 1127-41.
327. Salomon, R.M., et al., *MDMA (Ecstasy) association with impaired fMRI BOLD thalamic coherence and functional connectivity*. *Drug Alcohol Depend*, 2012. **120**(1-3): p. 41-7.
328. Selvaraj, S., et al., *Brain serotonin transporter binding in former users of MDMA ('ecstasy')*. *Br J Psychiatry*, 2009. **194**(4): p. 355-9.
329. Kish, S.J., et al., *Low striatal serotonin transporter protein in a human polydrug MDMA (ecstasy) user: a case study*. *J Psychopharmacol*, 2010. **24**(2): p. 281-4.
330. Erritzoe, D., et al., *In vivo imaging of cerebral serotonin transporter and serotonin(2A) receptor binding in 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") and hallucinogen users*. *Arch Gen Psychiatry*, 2011. **68**(6): p. 562-76.
331. Chang, L., et al., *Cerebral (1)H MRS alterations in recreational 3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy") users*. *J Magn Reson Imaging*, 1999. **10**(4): p. 521-6.
332. Cowan, R.L., et al., *Occipital cortical proton MRS at 4 Tesla in human moderate MDMA polydrug users*. *Psychiatry Res*, 2007.
333. Reneman, L., et al., *Reduced N-acetylaspartate levels in the frontal cortex of 3,4-methylenedioxymethamphetamine (Ecstasy) users: preliminary results*. *AJNR Am J Neuroradiol*, 2002. **23**(2): p. 231-7.
334. De Win, M., Jager, G., Reneman, L., Booij, J., van den Brink, W., Den Heeten, G., et al., *Ecstasy: Is It Safe for the Brain? First Prospective Study on Effects of Low Doses of Ecstasy on the Brain in New Ecstasy Users, Using a Combination of Advanced MR Imaging Techniques and [123I]β-CIT SPECT*, in *Radiological Society of North America (RSNA)*. 2006: Chicago, IL.
335. Klomp, A., et al., *The Effects of Ecstasy (MDMA) on Brain Serotonin Transporters Are*

- Dependent on Age-of-First Exposure in Recreational Users and Animals.* PLoS One, 2012. **7**(10): p. e47524.
336. Semple, D.M., et al., *Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users.* Br J Psychiatry, 1999. **175**: p. 63-9.
337. Gouzoulis-Mayfrank, E. and J. Daumann, *Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage?* Addiction, 2006. **101**(3): p. 348-61.
338. Buchert, R., et al., *A voxel-based PET investigation of the long-term effects of "Ecstasy" consumption on brain serotonin transporters.* Am J Psychiatry, 2004. **161**(7): p. 1181-9.
339. Gouzoulis-Mayfrank, E., et al., *Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users.* Prog Neuropsychopharmacol Biol Psychiatry, 2003. **27**(5): p. 819-27.
340. Daumann, J., Jr., et al., *Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study.* Biol Psychiatry, 2004. **56**(5): p. 349-55.
341. Gouzoulis-Mayfrank, E., et al., *Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use.* Drug Alcohol Depend, 2005. **78**(3): p. 317-23.
342. Buchert, R., et al., *Reversibility of ecstasy-induced reduction in serotonin transporter availability in polydrug ecstasy users.* Eur J Nucl Med Mol Imaging, 2006. **33**(2): p. 188-99.
343. Green, A.R., E. O'Shea, and M.I. Colado, *A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response.* Eur J Pharmacol, 2004. **500**(1-3): p. 3-13.
344. Hall, A.P. and J.A. Henry, *Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management.* Br J Anaesth, 2006. **96**(6): p. 678-85.
345. Cregg, M.T. and J.A. Tracey, *Ecstasy abuse in Ireland.* Ir Med J, 1993. **86**(4): p. 118-20.
346. Sadeghian, S., et al., *Two ecstasy-induced myocardial infarctions during a three month period in a young man.* Arch Iran Med, 2007. **10**(3): p. 409-12.
347. Kahn, D.E., N. Ferraro, and R.J. Benveniste, *3 cases of primary intracranial hemorrhage associated with "Molly", a purified form of 3,4-methylenedioxymethamphetamine (MDMA).* J Neurol Sci, 2012. **323**(1-2): p. 257-60.
348. Tan, B. and P. Foley, *Guttate psoriasis following Ecstasy ingestion.* Australas J Dermatol, 2004. **45**(3): p. 167-9.
349. Brand, H.S., S.N. Dun, and A.V. Nieuw Amerongen, *Ecstasy (MDMA) and oral health.* Br Dent J, 2008. **204**(2): p. 77-81.
350. Duxbury, A.J., *Ecstasy--dental implications.* Br Dent J, 1993. **175**(1): p. 38.
351. Nixon, P.J., C.C. Youngson, and A. Beese, *Tooth surface loss: does recreational drug use contribute?* Clin Oral Investig, 2002. **6**(2): p. 128-30.
352. Clark, A.D. and N. Butt, *Ecstasy-induced very severe aplastic anaemia complicated by invasive pulmonary mucormycosis treated with allogeneic peripheral blood progenitor cell transplant.* Clin Lab Haematol, 1997. **19**(4): p. 279-81.
353. Marsh, J.C., et al., *Aplastic anaemia following exposure to 3,4-methylenedioxymethamphetamine ('Ecstasy').* Br J Haematol, 1994. **88**(2): p. 281-5.
354. Mutlu, H., et al., *'Ecstasy'(MDMA)-induced pneumomediastinum and epidural*

- pneumatisis*. *Diagn Interv Radiol*, 2005. **11**(3): p. 150-1.
355. Onwudike, M., *Ecstasy induced retropharyngeal emphysema*. *J Accid Emerg Med*, 1996. **13**(5): p. 359-61.
356. Pittman, J.A. and J.C. Pounsford, *Spontaneous pneumomediastinum and Ecstasy abuse*. *J Accid Emerg Med*, 1997. **14**(5): p. 335-6.
357. Quin, G.I., G.M. McCarthy, and D.K. Harries, *Spontaneous pneumomediastinum and ecstasy abuse*. *J Accid Emerg Med*, 1999. **16**(5): p. 382.
358. O'Neill, D. and J.K. Dart, *Methylenedioxyamphetamine ('Ecstasy') associated keratopathy*. *Eye*, 1993. **7**(Pt 6): p. 805-6.
359. Schroeder, B. and S. Brieden, *Bilateral sixth nerve palsy associated with MDMA ("ecstasy") abuse*. *Am J Ophthalmol*, 2000. **129**(3): p. 408-9.
360. Beuerle, J.R. and F. Barrueto, Jr., *Neurogenic bladder and chronic urinary retention associated with MDMA abuse*. *J Med Toxicol*, 2008. **4**(2): p. 106-8.
361. Bryden, A.A., P.J. Rothwell, and P.H. O'Reilly, *Urinary retention with misuse of "ecstasy"*. *Bmj*, 1995. **310**(6978): p. 504.
362. Delgado, J.H., et al., *Acute, transient urinary retention from combined ecstasy and methamphetamine use*. *J Emerg Med*, 2004. **26**(2): p. 173-5.
363. Diffley, M., et al., *Catecholaminergic polymorphic ventricular tachycardia found in an adolescent after a methylenedioxymethamphetamine and marijuana-induced cardiac arrest*. *Crit Care Med*, 2012. **40**(7): p. 2223-6.
364. Hoggett, K., D. McCoubrie, and D.M. Fatovich, *Ecstasy-induced acute coronary syndrome: something to rave about*. *Emerg Med Australas*, 2012. **24**(3): p. 339-42.
365. Hua, Y.S., et al., *Contraction band necrosis in two ecstasy abusers: a latent lethal lesion associated with ecstasy*. *Am J Forensic Med Pathol*, 2009. **30**(3): p. 295-7.
366. Moller, M., et al., *Ecstasy-induced myocardial infarction in a teenager: rare complication of a widely used illicit drug*. *Clin Res Cardiol*, 2010. **99**(12): p. 849-51.
367. Sano, R., et al., *A fatal case of myocardial damage due to misuse of the "designer drug" MDMA*. *Leg Med (Tokyo)*, 2009. **11**(6): p. 294-7.
368. Toth, A.R. and T. Varga, *Myocardium and striated muscle damage caused by licit or illicit drugs*. *Leg Med (Tokyo)*, 2009. **11 Suppl 1**: p. S484-7.
369. Colak, Y., et al., *Ecstasy induced fatal hepatic failure*. *J Gastrointest Liver Dis*, 2011. **20**(2): p. 215-6.
370. Mikula, T., J. Kozłowska, and A. Wiercinska-Drapalo, *Alcohol and ecstasy (MDMA-3,4-methylenedioxymethamphetamine) overdose as a reason for acute hepatitis with gall bladder inflammation*. *Drug Alcohol Rev*, 2009. **28**(6): p. 685.
371. Mizia-Stec, K., et al., *Severe dilated cardiomyopathy as a consequence of Ecstasy intake*. *Cardiovasc Pathol*, 2008. **17**(4): p. 250-3.
372. De Smet, K., et al., *Bilateral globus pallidus infarcts in ecstasy use*. *JBR-BTR*, 2011. **94**(2): p. 93.
373. Gardner, H., et al., *Acute hippocampal sclerosis following ecstasy ingestion*. *Neurology*, 2009. **73**(7): p. 567-9.
374. Marchesi, C., M. Tonna, and C. Maggini, *Obsessive-compulsive disorder followed by psychotic episode in long-term ecstasy misuse*. *World J Biol Psychiatry*, 2009. **10**(4 Pt 2): p. 599-602.
375. Potash, M.N., K.A. Gordon, and K.L. Conrad, *Persistent Psychosis and Medical Complications After a Single Ingestion of MDMA "Ecstasy": A Case Report and Review of the Literature*. *Psychiatry (Edgmont)*, 2009. **6**(7): p. 40-4.

376. Tabatabaei, S.A., M. Soleimani, and A. Khodabandeh, *A case of autoenucleation associated with a contralateral field defect*. Orbit, 2011. **30**(3): p. 165-8.
377. Claffey, C., *A 26-year-old woman with sudden onset cerebral edema*. J Emerg Nurs, 2011. **37**(1): p. 55-6.
378. Ghatol, A. and A. Kazory, *Ecstasy-associated acute severe hyponatremia and cerebral edema: a role for osmotic diuresis?* J Emerg Med, 2012. **42**(6): p. e137-40.
379. Gritti, P., et al., *Are we aware of ecstasy effects?* Intern Emerg Med, 2009. **4**(2): p. 175-7.
380. Grunau, B.E., M.O. Wiens, and M. Greidanus, *Dantrolene for the treatment of MDMA toxicity*. CJEM, 2010. **12**(5): p. 457-9.
381. Russell, T., et al., *Ecstasy-induced delayed rhabdomyolysis and neuroleptic malignant syndrome in a patient with a novel variant in the ryanodine receptor type 1 gene*. Anaesthesia, 2012. **67**(9): p. 1021-4.
382. Vanden Eede, H., et al., *Rhabdomyolysis in MDMA intoxication: a rapid and underestimated killer. "Clean" Ecstasy, a safe party drug?* J Emerg Med, 2012. **42**(6): p. 655-8.
383. Islam, N., G.T. Plant, and J.F. Acheson, *Saccadic lateropulsion or ipsipulsion*. Acta Ophthalmol, 2008. **86**(6): p. 688-9.
384. Nifosi, F., et al., *Hippocampal remodelling after MDMA neurotoxicity: a single case study*. World J Biol Psychiatry, 2009. **10**(4 Pt 3): p. 961-8.
385. Wilcox, J.A. and A.H. Wilcox, *Movement disorders and MDMA abuse*. J Psychoactive Drugs, 2009. **41**(2): p. 203-4.
386. Gomez-Fernandez, C., et al., *Facial eruption related to snorting Ecstasy*. Eur J Dermatol, 2010. **20**(6): p. 853-4.
387. Shah, H.V., G.H. Irvine, and M. Bradley, *Rhabdomyolysis of the masseter muscle: case report*. Br J Oral Maxillofac Surg, 2008. **46**(2): p. 138-40.
388. Richman, J. and A. Ferber, *Severe aplastic anemia with hot pockets following daily Ecstasy ingestion*. Am J Hematol, 2008. **83**(4): p. 321-2.
389. Sauvageau, A., *Death from a possible anaphylactic reaction to ecstasy*. Clin Toxicol (Phila), 2008. **46**(2): p. 156.
390. Check, E., *Psychedelic drugs: the ups and downs of ecstasy*. Nature, 2004. **429**(6988): p. 126-8.
391. Doblin, R., *A clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): partnering with the FDA*. J Psychoactive Drugs, 2002. **34**(2): p. 185-94.
392. Randolph, C., *Repeatable Battery for the Assessment of Neuropsychological Status manual*. 1998, San Antonio, TX: The Psychological Corporation.
393. Roman, D.D., et al., *Extended norms for the paced auditory serial addition task*. Clin Neuropsychol, 1991. **5**(1): p. 33-40.
394. Gronwall, D.M., *Paced auditory serial-addition task: a measure of recovery from concussion*. Percept Mot Skills, 1977. **44**(2): p. 367-73.
395. Mitrushina, M.N., Boone K. B., and L.F. D'Elia, *Handbook of normative data for neuropsychological assessment*. 1999, New York, NY: Oxford University Press.
396. Blake, D.D., et al., *A clinician rating scale for assessing current and lifetime PTSD: the CAPS-1*. Behav Ther, 1990. **13**: p. 187-188.
397. Nagy, L.M., et al., *Open prospective trial of fluoxetine for posttraumatic stress disorder*. J Clin Psychopharmacol, 1993. **13**(2): p. 107-13.
398. Mithoefer, M.C., et al., *Safety, Efficacy and Durability of MDMA-Assisted Psychotherapy*

*in Subjects with Chronic, Treatment-Resistant Posttraumatic Stress Disorder: Completed and Ongoing Randomized, Controlled, Triple-blind Phase 2 Pilot Studies, in Military medical research across the continuum of care. 2012: Fort Lauderdale, FL.*

MAPS Study MP4  
Canada

Summary of Changes Amendment 1 Version 2  
June 20, 2013

## **PROTOCOL MP-4**

### **Summary of Changes**

IND #63,384

**Original:** March 17, 2009  
**Amendment 1 Version 1:** October 27, 2010  
**Amendment 1 Version 2:** June 20, 2013

### **A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada**

#### **SPONSOR**

Multidisciplinary Association for Psychedelic  
Studies (MAPS)  
309 Cedar Street, #2323  
Santa Cruz, CA 95060

#### **SPONSOR DESIGNEE**

[REDACTED]  
Phone number: [REDACTED]  
Ingrid Pacey, M.B.B.S., F.R.C.P.[C]  
Research Affiliate, CARBC  
University of Victoria  
3369 West 4<sup>th</sup> Avenue  
Vancouver, BC Canada  
V6R 1N6  
Tel: 604-732-9309

#### **CLINICAL INVESTIGATOR**

#### **MEDICAL MONITOR**

[REDACTED]

**For trial related emergencies, call: 650-248-4647**

## 1.0 MP4 Amendment 1 Version 2 Rationale

This amendment is being submitted prior to study start and is necessary due to the amount of time that passed between the original protocol approval to the time MAPS was allowed to import study drug. During the four years since the original approval the overall MDMA/PTSD development plan has progressed as studies have been completed, this amendment brings the protocol inline with the current Phase 2 program. This amendment reflects the most up to date study design, timing of treatment and selection of doses that MAPS is now investigating as part of the overall dose response investigation across multiple Phase 2 studies. The primary changes in Amendment 1 Version 2 effect the study design, cross over time point, timing of the primary endpoint, Stage 2 dosing and the addition of obfuscation to the informed consent. The primary changes are discussed below as well as in section 2.0. There are additional changes throughout the protocol that do not effect design but provide additional detail to procedures, provide clarifications or are administrative changes based on our new protocol template. A protocol in track changes is being provided as well as the summary of changes to document all changes in detail.

### 1.1 Summary of Design Changes

The protocol design has been amended to move the primary endpoint assessment of PTSD symptoms and unblinding from after the third experimental session to one-month after the second blinded experimental session. This change and the alignment of all study visit time points brings the study design into accordance with the timing of the primary endpoint and visits of other MDMA/PTSD Phase 2 studies in the clinical development plan.

Full dose subjects will still have three full dose experimental sessions as in the original approved protocol. The first two experimental sessions will be blinded. After unblinding, only full dose subjects will continue onto the 3<sup>rd</sup> experimental session and associated integrative sessions in Stage 1. Upon unblinding at the primary endpoint, subjects in the comparator dose group will cross over from Stage 1 to Stage 2 after two instead of three experimental sessions. Previously, unblinding was after the third experimental session at the two-month follow-up. Subjects who received the comparator dose during the blinded portion of the study will continue to have the opportunity to cross over to Stage 2 and receive three experimental sessions. Stage 2 procedures and schedule will be similar to Stage 1 but will be open label. The doses in Stage 2 have been amended from full dose MDMA to explore the optimal therapeutic dose of MDMA. Subjects in Stage 2 will receive an initial dose of 100 mg at the first experimental session, either an initial dose of 100 mg or 125 mg MDMA at the second and third experimental sessions based on the opinion of the therapist team. The supplemental doses for each session will be half of the initial dose, respectively.

The crossover is three months earlier than the previous protocol version that required three experimental sessions for all subjects in Stage 1. This was done to decrease the

amount of time comparator dose subjects spend in Stage 1 and to increase our ability to evaluate whether the treatment method will involve two rather than three experimental sessions. Based on our experience in previous studies, in those who have received a low or active placebo dose, we believe it is safe to administer three low dose sessions, but it may create an unnecessary hardship for subjects by extending their treatment at low and medium doses. We believe that only two sessions prior to unblinding are likely to demonstrate significant separation between the comparator dose group and the full dose group based on completed MDMA/PTSD studies sponsored by MAPS.

As a part of MAPS' ongoing efforts to optimize the double-blind of MDMA-assisted psychotherapy studies, subjects will be informed of the two groups that they may be randomly assigned to, but a level of obfuscation will be added to the informed consent process during the blinded portion of the study. The sponsor is currently exploring two approaches to successful maintenance of the double blind. One of these approaches is a dose-response design, which is already being tested in an ongoing MAPS-sponsored Phase 2 study in veterans and first responders in the USA. One complication of this approach is that confusion about the condition assignment is based on the subjective effects of the drug, which are likely to be proportional to the dose the subjects receive. If the subjective effects of the lower dose are large enough to confuse a subject about the dose they receive, the dose may also have some level of efficacy. One potential approach to this issue is to add obfuscation to the informed consent process in which subjects would be told they would receive either an inactive placebo or one of several doses of MDMA. Then subjects would be asked to guess if they received active MDMA or placebo to enable assessment of the double blind. In order for the lower dose to be confused with a full dose of MDMA, the informed consent form states that the comparator may or may not have MDMA. The obfuscation is for a limited period during treatment until subjects are fully debriefed upon unblinding after only two blinded drug-assisted sessions. The research cannot be practically conducted without this alteration to the protocol because obfuscation will make it possible for subjects to be less certain of the identity of the comparator.

A long-term follow up assessment has been added to the study, with symptoms assessed 1 year after a participant has had a final MDMA-assisted psychotherapy session. A number of secondary changes occurred in this amendment as a result of the addition of the long-term follow-up, including changes in wording and instructions concerning collection of adverse events and the use of a memory aid card for use between the final study visit and the long-term follow up assessment.

Finally, the protocol has been restructured. Some sections appear earlier in the Amendment than in the original protocol, and the section containing Pharmacology included in the original study protocol is omitted from the Amendment. Most of the information within the omitted section can be found in the 6<sup>th</sup> edition of the Investigator's Brochure. Changes were made to sections that are associated with the major changes discussed above these include updates to the protocol objectives, visit descriptions, time and events and analysis sections.

Obfuscation here

Grammatical changes were made throughout in order to accommodate the changes to the protocol. In addition, corrections to spelling and sentence structure have been updated for readability. These types of changes are not included in the change list below.

Due to the amount of changes in this protocol, a red-line version of the protocol will be provided to view exact changes.

## 2.0 Systematic Changes Effecting Multiple Sections

1. The PI has established Research Affiliate status with the Center for Addiction Research in British Columbia (CARBC) as a part of the University of Victoria in order to support qualifications for the study.
2. The study synopsis has been revised to match the Sponsor's new synopsis template, which no longer includes the inclusion/exclusion criteria and now includes protocol objectives, measures, procedures for recruitment and statistical analysis as well as an abbreviated study flowchart.
3. The Time and Events Table has been revised to match updated study procedures, and a new Summary of Events flowchart has been added to graphically depict study procedures.
4. Updated language throughout to match new template wording. Section numbers have been added to each section with numbers alongside headers, with the List of Abbreviations given the first number of 1.0, to provide a clear way to reference portions of the protocol. Rationale: This was done to make it easier to read and follow the protocol and to locate and reference specific sections of the protocol.
5. The protocol title has changed to reflect the study design. It is now titled "A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada"
6. A list of abbreviations now appears prior to the text of the protocol to provide clarity while reading the protocol.
7. "Principal investigator" and PI have been replaced by the terms "clinical investigator" and "CI" throughout the document.
8. Updated all sub-sections in 3.0 Background information with most recent scientific literature and results of clinical trials with MDMA-assisted psychotherapy for PTSD. Updated the purpose to be consistent with the new design.

9. A level of obfuscation was added to the informed consent process to better mask the blind. The ICF will state the probability of random assignment to the full dose group or the comparator dose group, however there will be a level of obfuscation, which makes it unclear that there is only one comparator dose of 50 mg of MDMA. The ICF will indicate the comparator dose may or may not contain MDMA. If subjects ask about the composition of investigational product in the comparator dose group, the exact contents of the comparator dose will be said to include lactose and may or may not include MDMA, however everyone assigned to the comparator dose group will have the opportunity to receive full dose MDMA during Stage 2. For all subjects in the comparator dose group, the content of the comparator dose will be disclosed after the primary endpoint assessments when unblinding occurs. Section 5.0 on Informed Consent has been revised to include this information as well as procedures for withdrawal of consent. The informed consent quiz has been removed in line with current procedures in MAPS-sponsored studies. Subjects will complete the informed consent process with the PI to ensure that accurate and thorough information is provided about the study in verbal and written form.
10. The plan for subject recruitment has been updated to reflect how this will be conducted for the subject population. Recruitment will now include the use of advertisements and announcements on internet sites, including the sponsor site.
11. Clarity was added to the overall study objective in light of completed studies of MDMA-assisted psychotherapy and the development of a Treatment Manual. Study Objectives have been rewritten so that there is a single primary study objective and so that secondary objectives address newly added measures.
12. The Primary Objective has been updated to reflect the unblinding at the primary endpoint after the second experimental session.

Previously: "Assess changes in PTSD symptoms as measured via Clinician-Administered PTSD Scale (CAPS) scores in Stage 1 in participants receiving the active placebo vs. full dose of MDMA-assisted psychotherapy."

Now: "Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session. This update was to reflect the unblinding at the primary endpoint after the second experimental session."

13. The Secondary Objectives were updated to reflect the unblinding at the primary endpoint after the second experimental session. Additional secondary objectives describing process measures were added regarding adherence to the Treatment manual, belief of condition assignment, testing the two vs. three session treatment

model, and exploration of the role of non-ordinary states of consciousness immediately after experimental sessions.

14. The Safety Objectives were updated to reflect the unblinding at the primary endpoint after the second experimental session and the proper assessment timeline to support the updated primary endpoint, but also added the Visual Analog Scale to collect changes to pre-existing tinnitus and/or chronic pain symptoms, specifically in subjects with a medical history of tinnitus and/or chronic pain. Objectives related to the RBANS and PASAT were moved from outcome measures to safety measures to appropriately reflect the goal of assessing neurocognitive function after MDMA-assisted psychotherapy. The safety objective concerning measures of cognitive function has been revised with the study design.
15. The RBANS and PASAT will be administered at a third visit two months after the third Stage 1 or Stage 2 session to assess the safety effects of MDMA in people who have all received full dose MDMA during the course of the study. The measures of cognitive function will be assessed via RBANS and PASAT again two months after the third Stage 1/Stage 2 experimental sessions in addition to baseline and primary endpoint assessments. The administration of a repeatable test battery will confirm and extend data concerning any potential effects of MDMA on cognitive function. At the secondary endpoint, most participants will have had received the maximum cumulative exposure of MDMA for the study.
16. The addition of the following assessments:
  - DES-II: Dissociation Experiences Scale II- The DES-II is a 28-item self-report measure of dissociation, defined as a lack of normal integration of an individual's thoughts, feelings, or experiences into the stream of consciousness or memory. It is an established measure of dissociative symptoms. The DES-II can also be used to produce scores for three factors, amnesia, depersonalization, and derealization. The scale differentiated between respondents without psychiatric disorders or with psychiatric disorders with few dissociative symptoms and respondents with psychiatric disorders associated with dissociative symptoms. Subjects will complete the DES-II at the same time as the CAPS is administered according to the Time and Events Table. Dissociation and depersonalization are likely to be added to symptoms of PTSD with the upcoming revision of the DSM, DSM-V. In order to compare the prevalence of these symptoms to future studies that may use the DSM-V, this secondary measure will be used.
  - The NEO-PI (Neuroticism-Extroversion-Openness Personality Inventory-Revised) will serve as a measurement of personality. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with

sound properties of reliability and validity that operationally define personality structure according to a five-factor model.

- **PSQI: Pittsburgh Sleep Quality Index-** The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of self-reported sleep quality over a one-month period. The PSQI was designed to be a reliable, standardized measure able to distinguish between good and poor sleepers.
- **SOCQ: States of Consciousness Questionnaire-** The SOCQ is a 100-item questionnaire based on the “Peak Experience Profile” designed by Pahnke and colleagues. It has seven subscale scores; internal unity, external unity, transcendence of time and space, ineffability and paradoxicality (claim of difficulty in describing the experience in words), sense of sacredness, noetic quality, and deeply felt positive mood. Subjects will complete the SOCQ after each experimental session, at any time between the end of an experimental session and prior to leaving the treatment facility the next day, and results will inform comparison of MDMA to the subjective effects other psychoactive drugs that have been studied with this measure.
- **Changes in Tinnitus or Pain using the Visual Analog Scale:** A 100-millimeter visual analog scale will be used to assess changes in symptoms of pre-existing tinnitus and/or chronic pain. The changes in Tinnitus and/or Pain visual analog scale will allow rating of symptom severity from “None” to “Worst Case Imaginable”. This exploratory measure will enable quantification of subjective somatic symptoms that are known to be associated with PTSD. Presence of chronic pain is associated with PTSD, possibly as a result of psychological response to traumatic stress as reflected in brain activity, such as increased amygdalar activity in response to pain and transmitter systems involved in the stress response. Changes will be collected in subjects presenting with a history of either. PTSD, chronic pain, and tinnitus are frequently co-morbid. In order to track the prevalence and variation in symptom severity of chronic pain and tinnitus symptoms for accurate collection of any exacerbations as Adverse Events, or any improvements in the symptoms as a result of study participation, this new measure has been added.
- **Perceptions of experimental sessions:** Perceptions of the experimental sessions will be collected from each full dose subject during the primary endpoint visit after unblinding and from Stage 2 subjects during the secondary endpoint visit in Stage 2 before the third experimental session in Stage 1/Stage 2. Perceptions will be collected again at the end of Stage 1/Stage 2. These perceptions are collected as a part of the sponsor’s ongoing initiative to assess the therapeutic value of the third experimental session and information on the optimal therapeutic dose of MDMA.

- The Post Traumatic Growth Inventory (PTGI) is a 21-item self-report measure of perceived growth or benefits occurring after a traumatic event. It contains five subscales; relationship to others, new possibilities, personal strength, spiritual change, and appreciation of life [133, 134]. In this study, subjects will complete the PTGI in reference to the time since the trauma at baseline, but will respond in reference to the beginning of their participation in the study on all subsequent occasions.
- Adherence criteria and competence ratings will be conducted by qualified, trained blinded adherence raters who will analyze video data from selected preparatory, experimental and integrative sessions. The elements included in adherence criteria are specific to each type of session. These ratings will be collected, at minimum, for each therapist team in the study. The goal of these ratings will be to correlate therapist adherence to the treatment manual with outcome as a part of the sponsor's ongoing efforts to standardize treatment methods of MDMA-assisted psychotherapy for PTSD.
- The revised Beck Depression Inventory, or BDI-II, will be used in place of the BDI.
- The Global Assessment of Function (GAF) is a measure of general function made through clinical observation. The GAF consists of a single score, ranging from 0 to 100, with 100 reflecting superior function and 0 reflecting serious risk of causing harm to the self or others.
- The NEO-PI will serve as a measurement of personality. The NEO-PI is a 240-item self-report assessment that takes between 30 and 40 minutes to complete. It is a well-established measure of five personality traits with sound properties of reliability and validity that operationally define personality structure according to a five-factor model.
- The suicidality assessment Adult Suicide Ideation Questionnaire (ASIQ) will be replaced with the Columbia Suicide Severity Rating Scale (C-SSRS), and it will be administered more frequently than in the original study design, according to U.S. FDA requirements for psychiatric clinical trials. The C-SSRS is a clinician-administered measure of suicidal behavior devised to detect potential suicidal thoughts or behaviors during a clinical trial. The C-SSRS will be performed by the PI at baseline, and repeated throughout the protocol to assess suicidality.
- The long-term follow-up assessment will include a questionnaire concerning perceived benefits and harms of study participation and views concerning study participation.

12. Changed the comparator dose from 25 mg with an optional 12.5mg supplemental dose to 50 mg with an optional 25mg supplemental dose. Changed wording describing the lower dose from “Active Placebo” to “Comparator Dose” for consistency amongst protocols in describing the slightly higher 50mg dose. This change was made in line with the sponsor’s progression through the clinical development plan and completion of a study with the 25mg active placebo dose in the interim of the approval process for this study. Section 12.1 Statistical Power was updated to reflect the estimated effect size based on completed studies.
13. Defined and clarified treatment resistant subjects as those who “were unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to either:
  - a. Inability to tolerate psychotherapy for PTSD (e.g. persistent “over-engagement” when attempting Prolonged Exposure Therapy).
  - b. Inability to tolerate psychopharmacology for PTSD due to treatment-emergent side effects;”
11. Addition of five new inclusion criteria of subjects who “Are willing to provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by Clinical Investigators in the event of a subject becoming suicidal; those who “Agree to inform the Clinical Investigators within 48 hours of any planned medical interventions;” those who “Agree to have all clinic visit sessions recorded to audio and video;” those who “Agree not to participate in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period.” and those who “Are at least 21 years old.” These criteria were added to ensure that the results of the study are clearly attributed to the investigational treatment, that the recruitment population is clearly captured in the criteria, and that subjects are willing to share personal and medical information with the investigators.
14. Revision of the inclusion criterion for subjects who “Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control” to also allow for subjects “on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for ten days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician.” Instructions for medication tapering were added to Section 14.4 in the form of a table and additional wording describing the timing of preparatory sessions with medication tapering was added to Section 7.3 Study Duration and Visit Windows.
15. Addition of one exclusion criterion #12, those who “Have any current problem, which in the opinion of the Principal Clinical Investigator or Medical Monitor,

- might interfere with participation in the study.” The sponsor is continuing to refine exclusion criteria for the treatment in preparation for Phase 3 studies, and will collect information on problems that may interfere with treatment through this criterion.
16. Moved unblinding to after the second experimental session, rather than the third. This was done to decrease the amount of time comparator dose subjects spend in Stage 1 and to increase our ability to evaluate whether our treatment method will involve two rather than three experimental sessions.
  17. CAPS score was raised to 60 from 50. The CAPS score cutoff was raised to 60 in order to work with more severe PTSD cases and to avoid floor effects.
  18. The Amendment clarifies that a single consent form will cover Stage 1 and Stage 2. The revision was made so that enrollment includes the possibility of entering stage 2. Subjects who are eligible for stage 2 and do not wish to enroll can withdraw from the study.
  19. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Stage 2 follows similar procedures and visit schedule as Stage 1 using varied active doses of MDMA, in which each initial dose may be followed by a supplemental dose that will be half of the initial dose. In Stage 2, subjects will receive an initial dose of 100 mg MDMA during the first experimental session. The co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg MDMA in the second and third experimental sessions.
  20. The amounts of MDMA encapsulated for Stage 1 has been updated to: 125 mg, 62.5 mg, 50 mg, and 12.5 mg. Previously, 125 mg, 62.5 mg, 50 mg, and 25 mg, were to be created. Section 8.0 has been revised to accommodate changes in dosing strategy for Stage 1 and Stage 2. New tables and text were provided for clarity to describe the various doses of study drug to be employed, and drug labels were revised in accordance with Health Canada regulations.
  21. Section 9.1 and 9.2 were revised to match the Sponsor’s new web-based randomization program requirements that will enable real-time drug accountability and randomization tracking.
  22. Reference to Emergency Unblinding Envelopes has been removed, as the site should now contact the sponsor, if needed. If there is an emergency requiring knowledge of subject’s condition assignment, the blind may be broken for an individual subject. The investigator may be provided with the condition assignment in case of emergency through the web-based randomization system. At any time the unblinded Randomization Monitor can be contacted if assistance is needed.

23. Section 9.4 Visit Descriptions have been re-written for clarity and to align with the new study design and assessments.
24. Section 10.0 "Removal of Subjects from Therapy or Assessment" has been updated with language to provide clarification on study procedures relating to collecting follow-up data on subjects removed from the study. Subjects removed from the study may still be assessed at long-term follow up if possible for an intent-to-treat analysis. This analysis will address the potential that outcomes for the study will only be assessed in subjects who are likely to complete the study.
25. Section 12.0 Data Analysis has been updated to reflect the new study design and primary and secondary endpoints.
26. Section 12.1 Statistical Power has been revised to calculate power using comparator dose and full dose and information drawn from publications of data from sponsor-supported studies. The statistical power has been updated to reflect new information concerning sponsor-supported research and the comparator dose.
27. Section 13.0 is no longer titled "Monitoring for Toxicity". Plans for Risk Mitigation were moved from the Appendix to Section 13.0, and it is now titled "Risk Mitigation". The section was shortened to include only relevant information to the protocol. All other more specific and in-depth information is contained in the Investigator's Brochure. In line with recently completed and published MDMA/PTSD studies, the potential for toxicity during experimental sessions was found to be minimal and adequately covered under Section 16.0 "Risks of Participation," Likewise, Section 13.1 "Medical Emergencies" has been updated with information on number of experimental sessions and that adverse events during sponsor-supported studies generally resolved without requiring medical intervention.
28. Section 14.0 "Adverse Events" has updated contact information for medical monitors, describes the use of memory aid cards for the interval between final stage 1 or stage 2 visits and long-term follow up, and details the types of adverse events collected during the course of the study. The AE collection information was updated to provide information related to study staff and requirements for AE collection during the long term follow up. In addition, all AEs related to changes in psychiatric status will be collected throughout the study to provide for further capturing of psychiatric AEs.
29. Section 14.3, previously titled "Commonly Expected Side Effects" is now titled "Spontaneously Reported Reactions." These expected reactions were updated with the most recent information and MDMA program collection. They are referred to as reactions with the understanding that the side effect profile of MDMA-assisted psychotherapy will only be determined post-approval.
30. Concomitant Medication collection and tapering instructions have been updated. A table containing commonly prescribed psychiatric medications and their half-

- lives is provided. Memory aid card information is now provided. This section has been updated to match the amended AE collections, particularly during the interval after the final stage 1 or stage 2 site visit and long-term follow up, and to provide clarity and information on all medications and tapering of pre-study medications throughout the protocol. The table permits informed estimation of appropriate tapering procedures.
31. Section 14.5 Clinical Laboratory Assessments has been updated to reflect the full panel of tests to be performed for thorough medical evaluation prior to enrollment and accurate assessment of adverse events that could be related to treatment.
  32. Section 15.0 Study Monitoring, Auditing and Documentation has been updated with new template language. Language was added to this section to provide consistency across MAPS studies and compliance with GCP.
  33. Section 16 "Risks of Participation" has been revised for clarification, to include risk mitigation information previously under other sections and to encompass the literature and data from Sponsor-supported research. The risk section contains relevant information on the risks of receiving MDMA. Information originally in "Risk Mitigation" is contained within this section.
  34. The section "Risk/Benefit Analysis" is no longer present in the protocol. The section was removed in line with sponsor protocol template design. The risks and benefits of the research are detailed in the "Introduction" and "Risks" sections. A thorough Risk/Benefit Analysis is not possible in a single pilot study with this sample size, and would be influenced by findings from multiple studies. As such, the Risk/Benefit Analysis will be conducted on an ongoing basis across multiple Phase 2 studies supported by the sponsor and is likely to change across the duration of this study.
  35. Section 18.0 Confidentiality was revised to reflect the Sponsor's updated procedures and requirements for ensuring confidentiality of study data kept in digital media.
  36. Section 22.0 Record Retention describing the conditions of record storage and responsibilities of the investigator concerning length of record retention has been added in compliance with agency regulations.
  37. Section 21.0 "Publication Policy" was added to the protocol to include the Sponsor's updated publication policy in line with previous and future publications of Phase 2 pilot studies in the clinical development plan.
  38. The section that was previously Chemistry and Manufacturing and Control has been removed as it is contained in the Investigator's Brochure in line with the sponsor's new protocol template.

39. Appendices describing facilities and visit by visit descriptions have been removed from the protocol. Study procedures are now described in a visit by visit fashion to improve compliance with the protocol. Facilities are only listed in the title page and are no longer part of the protocol template.
40. Draft case report forms are no longer present as an appendix. Draft case report forms are no longer part of the protocol template as the sponsor plans on utilizing Electronic Data Capture (EDC) for this study.

MAPS Study MP-4  
Canada

Amendment 1 Version 2  
June 20, 2013

**PROTOCOL MP-4**  
**IND #63,384**

**Original Protocol:** March 17, 2009  
**Amendment 1 Version 1:** October 27, 2010  
**Amendment 1 Version 2:** June 20, 2013

**A Randomized, Double-Blind, Dose Comparison Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD) - Canada**

**SPONSOR**

Multidisciplinary Association for Psychedelic Studies (MAPS),  
309 Cedar Street, #2323  
Santa Cruz, CA 95060

**SPONSOR DESIGNEE**

**CLINICAL INVESTIGATOR**

Ingrid Pacey, M.B.B.S., F.R.C.P.[C]  
Research Affiliate, CARBC  
University of Victoria  
3369 West 4<sup>th</sup> Avenue  
Vancouver, BC Canada  
V6R 1N6  
Tel: 604-732-9309

**MEDICAL MONITOR**

**For trial related emergencies, call: 650-248-4647**

- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** Active Placebo-controlled
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:**
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** -
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (To be submitted to Ethics Board Health Canada and, if approved, to FDA under IND#63,384)
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** .
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** 3 Francis
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** Belmont, MA 02478
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** PRINCIPAL INVESTIGATOR
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** Ingrid Pacey MBBS FRCP[C]
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** MEDICAL MONITOR
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:**
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** STUDY PERSONNEL
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** Andrew Feldmar MA  
Co-therapist investigator
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** V6S 1G5
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** Canada
- Berra Yazar 7/18/13 11:43 AM  
**Deleted:** STUDY MONITOR [CRA] ... [1]
- Unknown  
**Deleted:** .

**Table of Contents**

**1.0 List of Abbreviations ..... 4**

**2.0 Introduction ..... 6**

**3.0 Background ..... 7**

    3.1 Posttraumatic Stress Disorder ..... 7

    3.2 MDMA ..... 9

    3.3 Previous Clinical Experience with MDMA ..... 9

    3.4 MDMA-assisted Psychotherapy for PTSD ..... 11

    3.5 Purpose ..... 13

**4.0 Ethics ..... 13**

**5.0 Informed Consent ..... 14**

**6.0 Study Objectives ..... 15**

    6.1 Primary Objective ..... 15

    6.2 Secondary Objectives ..... 15

    6.3 Safety Objectives ..... 16

**7.0 General Investigational Plan ..... 17**

    7.1 Recruitment and Subject Population ..... 17

    7.2 Enrollment Criteria ..... 17

        7.2.1 Inclusion Criteria ..... 17

        7.2.2 Exclusion Criteria ..... 19

    7.3 Planned Duration of Study and Visit Windows ..... 20

**8.0 Drug Description and Dosage ..... 20**

    8.1 MDMA Compounding, Doses, and Labeling ..... 22

    8.2 MDMA Accountability ..... 24

    8.3 MDMA Storage and Handling ..... 24

**9.0 Method ..... 25**

    9.1 Randomization ..... 26

    9.2 Subject Numbering ..... 26

    9.3 Assessments and Measures ..... 30

        9.3.1 Outcome Measures ..... 30

        9.3.2 Safety Measures ..... 32

        9.3.3 Process Measures ..... 34

    9.4 Visit Descriptions ..... 35

        9.4.1 Prescreening, Screening, and Baseline Evaluation (Pre-study) ..... 35

        9.4.2 Preparatory Psychotherapy Sessions - Visits 1, 2, 3 (Stage 1), 18 (Stage 2) ..... 37

        9.4.3 Experimental Sessions - Visits 4, 8 (Stage 1), 13, (Full Dose Group Stage 1), 19, 23, 28 (Stage 2) ..... 39

        9.4.4 Integrative Sessions 24 Hours after Experimental Session - Visits 5, 9 (Stage 1), 14 (Full Dose Group Stage 1), 20, 24, 29 (Stage 2) ..... 42

        9.4.5 A Week of Daily Contact ..... 43

        9.4.6 Integrative Psychotherapy Between Experimental Sessions - Visits 6, 7, 10, 11, (Stage 1), 15, 16, (Full Dose Group Stage 1), 21, 22, 25, 26, 30, 31 (Stage 2) ..... 44

        9.4.7 Evaluation at Primary Endpoint and Unblinding - Visit 12 (Stage 1) ..... 45

        9.4.8 End of Stage 1 - Visit 17 (Full Dose Group Stage 1) ..... 46

        9.4.9 Open-label Stage 2 (Comparator Dose Subjects from Stage 1) ..... 46

        9.4.9 Long-term Follow-up ..... 47

**10.0 Removal of Subjects from Therapy or Assessment ..... 48**

**11.0 Premature Discontinuation of the Study ..... 49**

**12.0 Data Analysis ..... 49**

    12.1 Statistical Power ..... 51

**13.0 Risk Mitigation ..... 52**

    13.1 Medical Emergencies ..... 52

**14.0 Adverse Events ..... 53**

    14.1 Serious Adverse Events ..... 54

Berna Yazari 7/18/13 11:43 AM

**Deleted: Introductory Statement - 34**

    Background - 76

    PTSD and MDMA-assisted psychotherapy - 87

    Previous Clinical Experience with MDMA - 9

    Summary - 910

    Principal Investigator - 911

**Ethics - 912**

    Informed Consent of Subject - 912

**Study Objectives - 913**

**General Investigational Plan - 914**

    Study Population and Characteristics - 914

    Inclusion Criteria - 914

    Exclusion Criteria - 916

    Planned Duration of Study - 917

    Drug Description and Dosage - 917

    Method - 918

    Assessments and Measures - 921

**Visit Descriptions - 1023**

    Initial Screening and Diagnostic Evaluation - 1023

    Subject Numbering - 1023

    Enrollment and Baseline Evaluation - 1023

    Randomization - 1023

    Psychotherapy - 1024

    Introductory Sessions - 1024

    MDMA-assisted Psychotherapy - 1024

    Integrative Psychotherapy - 4228

    Evaluation Six weeks after the Third experimental session - 4329

    Unblinding and Opportunity for Participants in Active Placebo Condition Enroll in Open-Label Study Segment ("Stage 2") - 4329

    Open-Label Study Segment for Active Placebo Participants ("Stage 2") - 4330

    Assessment Six weeks after Third Open-Label Session - 4330

    Removal of Subjects from Therapy or Assessment - 4330

    Premature Discontinuation of the Study - 4331

    Data Analysis - 4331

    Statistical power - 4332

**Monitoring for Toxicity - 4332**

    Hypertension and related cardiovascular Effects - 4333

    Angina or Myocardial Infarction: - 4333

    Stroke: - 4334

    Psychological Distress: - 4334

    Dehydration: - 4336

    Hyponatremia: - 4336

    Liver toxicity: - 4336

    Neuropsychological toxicity: - 4336

    Abuse and dependence: - 4337

    Medical Emergencies - 5037

    Serious Adverse Events - 5438

    Adverse Event Collection - 5439

    Collection of Concomitant Medications - 5539

    Laboratory Assessments - 5540

    Study Monitoring, Auditing and Documentation - 5540

**Risks and Discomforts - 5540**

    Risks and Discomforts Associated with Drawing Blood - 5540

    Risks and Discomforts Associated with Screening Procedure - 5540

    Risks and Discomforts Associated with Non-Experimental and Experimental Psychotherapy - 5541

    Cardiovascular and Sympathomimetic Effects - 6142

... [2]

14.2 Adverse Event Collection .....	54
14.3 Spontaneously Reported Reactions .....	56
14.4 Collection of Concomitant Medications and Tapering Instructions.....	56
14.5 Clinical Laboratory Assessments .....	58
<b>15.0 Study Monitoring, Auditing, and Documentation .....</b>	<b>59</b>
<b>16.0 Risks of Participation.....</b>	<b>59</b>
16.1 Risks and Discomforts Associated with Psychotherapy Sessions and Assessment of Measures.....	59
16.2 Risks of Receiving MDMA.....	60
16.2.1 Cardiovascular and Sympathomimetic Effects .....	61
16.2.2 Psychological Distress.....	62
16.2.3 Body Temperature.....	64
16.2.4 Reproductive and Developmental Risks .....	65
16.2.5 Potential Neurotoxicity Associated with Ecstasy Use .....	65
16.3 Abuse Liability .....	65
16.4 Risks and Discomforts of Receiving the Comparator Dose of Study Drug .....	66
<b>17.0 Alternative Treatments and Procedures.....</b>	<b>66</b>
<b>18.0 Confidentiality.....</b>	<b>67</b>
<b>19.0 Costs to Subjects.....</b>	<b>68</b>
<b>20.0 Record Retention.....</b>	<b>68</b>
<b>21.0 Publication Policy.....</b>	<b>68</b>
<b>22.0 References.....</b>	<b>70</b>

▼

Berna Yazari 7/18/13 11:43 AM

**Deleted:**

**Introductory Statement**  
 This proposed Canadian pilot study is a randomized, double-blind, active placebo controlled evaluation of the safety and efficacy of MDMA-assisted psychotherapy in twelve patients with treatment-resistant posttraumatic stress disorder (PTSD). This study has been designed as part of an international, multi-site program of research sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS, www.maps.org), a USA-based non-profit research and educational organization. MAPS' long-term goal is to develop MDMA into a prescription medication approved by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Health Canada. MAPS is currently the only organization in the world of which we are aware sponsoring research into the therapeutic potential of MDMA.

**MAPS is currently sponsoring under FDA IND #63,384 a nearly completed pilot study of MDMA-assisted psychotherapy in 21 patients with treatment-resistant posttraumatic stress disorder (PTSD), taking place in Charleston, South Carolina under the direction of Dr. Michael Mithoefer. Twenty out of 21 subjects have already completed the protocol. The final experimental session for the 21<sup>st</sup> subject occurred on July 18, 2008 and the final two-month follow-up evaluation will take place around September 18, concluding the study. Preliminary results are remarkably promising with no drug-related Serious Adverse Events (SAEs) and statistically significant results supporting the efficacy of MDMA-assisted psychotherapy**

## **1.0 List of Abbreviations**

AE(s)	Adverse Event(s)
AED	Automated External Defibrillator
A:G	Albumin : Globulin ratio
ALT/SGPT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
AST/SGOT	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory II
BP	Blood Pressure
BT	Body Temperature
BUN	Blood Urea Nitrogen
C	Celsius
CAPS	Clinician Administered PTSD Scale
CI	Clinical Investigator(s) (e.g. therapists, co-Clinical Investigators)
CPK	Creatine phosphokinase
CPT	Cognitive Processing Therapy
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic Blood Pressure
DEA	Drug Enforcement Administration
DES-II	Dissociation Experiences Scale II
DMF	Drug Master File
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
ECG/EKG	Electrocardiogram
ED	Emergency Department
EMDR	Eye Movement Desensitization and Reprocessing
EMS	Emergency Medical Services
F	Fahrenheit
FDA	Food and Drug Administration
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
HCl	Hydrochloride
HIPA	Health Information Protection Act
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IR	Independent Rater
IRB	Institutional Review Board
ISF	Clinical Investigator Site File
IV	Intra-venous
LSD	d-Lysergic acid diethylamide

MAPS Study MP-4  
Canada

Amendment 1 Version 2  
June 20, 2013

MAOI	<u>Monoamine oxidase Inhibitor</u>
MAPS	<u>Multidisciplinary Association for Psychedelic Studies</u>
MCH	<u>Mean Corpuscular Hemoglobin</u>
MCHC	<u>Mean Corpuscular Hemoglobin Concentration</u>
MCV	<u>Mean Corpuscular Volume</u>
MDMA	<u>3,4-Methylenedioxymethamphetamine</u>
MP-1	<u>MAPS' First Clinical Trial of MDMA-assisted Psychotherapy for PTSD</u>
MP-2	<u>MAPS' Second Clinical Trial of MDMA-assisted Psychotherapy for PTSD</u>
NEO-PI	<u>Neuroticism Extroversion Openness Personality Inventory</u>
OT	<u>Oxytocin</u>
PASAT	<u>Paced Auditory Serial Addition Test</u>
PDS	<u>PTSD Diagnostic Scale</u>
PI	<u>Principal Clinical Investigator</u>
PRN	<u>As Needed</u>
PSQI	<u>Pittsburgh Sleep Quality Index</u>
PTSD	<u>Posttraumatic Stress Disorder</u>
PTCA	<u>Percutaneous Transluminal Coronary Angioplasty</u>
PTGI	<u>Posttraumatic Growth Inventory</u>
PTSD	<u>Posttraumatic Stress Disorder</u>
PTT	<u>Partial Thromboplastin Time</u>
RBANS	<u>Repeatable Battery for the Assessment of Neuropsychological Status</u>
RBC	<u>Red Blood Cell Count</u>
RDW	<u>Red Cell Distribution Width</u>
RRPQ	<u>Reactions to Research Participation Questionnaire</u>
SAE(s)	<u>Serious Adverse Event(s)</u>
SBP	<u>Systolic Blood Pressure</u>
SCID-I-RV	<u>Structured Clinical Interview for Diagnoses Axis I Research Version</u>
SERT	<u>Serotonin Transporter</u>
SL	<u>Sublingual</u>
SNRI	<u>Serotonin Norepinephrine Reuptake Inhibitor</u>
SOP(s)	<u>Standard Operating Procedure(s)</u>
SSRI	<u>Selective Serotonin Reuptake Inhibitor</u>
SUD	<u>Subjective Units of Distress</u>
T3	<u>Triiodothyronine</u>
T4	<u>Thyroxine</u>
TSH	<u>Thyroid Stimulating Hormones</u>
U.S.	<u>United States of America</u>
WBC	<u>White Blood Cell Count</u>

## 2.0 Introduction

The Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organization working to obtain approval for the prescription use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with chronic treatment-resistant posttraumatic stress disorder (PTSD). This study, seeking to test MDMA-assisted psychotherapy in Canadian residents with chronic treatment-resistant PTSD, is part of an international series of Phase 2 clinical trials. Ongoing and planned Phase 2 studies are laying the groundwork for a possible End-of-Phase 2 meeting with FDA and Phase 3 multi-site studies.

MAPS has published results indicating sustained improvements in PTSD severity after MDMA-assisted psychotherapy [1-3]. MAPS is currently conducting a U.S.-based Phase 2 trial treating U.S. military veterans, firefighters, and police officers with service-related, chronic, treatment-resistant PTSD, a U.S. Phase 2 pilot study in 12 subjects in Boulder, Colorado, and an Israeli Phase 2 pilot study in 10 subjects. Taken together, these pilot studies will help to gather preliminary data about the safety and efficacy of MDMA-assisted psychotherapy that will inform the design of possible Phase 3 multi-site studies.

This Canadian pilot study is a randomized, double-blind, dose comparison evaluation of MDMA-assisted psychotherapy in 12 patients with chronic, treatment-resistant PTSD. PTSD must be of at least 6 months duration without remission from prior treatment with either pharmacotherapy or psychotherapy of adequate dose/duration or where treatment was discontinued due to lack of tolerability. This study is designed to obtain estimates of effect size for safety and efficacy. The data will be combined with ongoing Phase 2 dose response studies in a meta-analysis.

This pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, seven of 12 people will receive a dose of MDMA expected to be fully therapeutic (full dose) and five of 12 will receive a comparator dose of MDMA during the blinded part of the study, referred to as Stage 1. PTSD and associated symptoms will be assessed at baseline and one month after the second double-blind MDMA-assisted (experimental) psychotherapy session. Cognitive function will also be assessed at baseline and again one month after the second experimental session. Study subjects will receive psychotherapy before and after each experimental session.

Unblinding will take place after the primary endpoint assessments. Full dose subjects will continue in Stage 1 and receive a third MDMA-assisted (experimental) psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over and take part in a second study segment, referred to as Stage 2, with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy. Stage 2 follows similar procedures and visit schedule as Stage 1 using varied active doses of MDMA, in which each initial dose

Unknown

Field Code Changed

Berra Yazar 7/18/13 11:43 AM

Deleted: (Wagner 2008, personal communication)

Berra Yazar 7/18/13 11:43 AM

Deleted: A separate longer-term follow-up of participants a year or more after study participation has been approved by our IRB and will be initiated soon. -

MAPS is sponsoring two additional ongoing pilot studies of MDMA-assisted psychotherapy in patients with PTSD, one in Switzerland under the direction of Dr. Peter Oehen, and one in Israel, under the direction of Dr. Moshe Kotler, Chair, Department of Psychiatry, Tel Aviv University, Sackler School of Medicine, and former Chief Psychiatrist of the Israeli Defense Forces. Both of these studies are designed for twelve subjects and are scheduled to be completed before the end of 2009. All studies are using the same primary outcome variable, the Clinician Administered PTSD Scale (CAPS), enabling examination of results across all studies, and meta-analyses of data pooled across each pilot study. All of MAPS' studies conducted outside of the US have been approved by regulatory authorities in those countries and have been submitted to FDA and are also being conducted under FDA IND 63,384. -

MAPS has also helped initiate and fund an FDA-approved study investigating MDMA-assisted psychotherapy in people with anxiety related to advanced-stage cancer. This study is taking place at Harvard Medical School's McLean Hospital, under the direction of Dr. John Halpern MD, the Sponsor/Investigator. The second of twelve subjects has been enrolled. The first subject has completed the study safely with reports of reduced anxiety and pain

may be followed by a supplemental dose that will be half of the initial dose. In Stage 2, subjects will receive an initial dose of 100 mg MDMA during the first experimental session. The co-therapists, in consultation with the subject, will decide whether to administer an initial dose of 100 mg or 125 mg MDMA in the second and third experimental sessions.

### 3.0 Background

#### 3.1 Posttraumatic Stress Disorder

PTSD is a debilitating psychiatric disorder arising after a traumatic life event. PTSD severely reduces quality of life and may directly or indirectly lead to or exacerbate other psychiatric and medical problems. A complex biopsychosocial condition, PTSD is characterized by a combination of three types of symptoms:

1. Hyperarousal symptoms such as hypervigilance, anxiety, and sleep disturbance.
2. Intrusive re-experiencing of traumatic experiences, such as intrusive memories, nightmares, or flashbacks.
3. Avoidance symptoms, including emotional numbing and withdrawal [4, 5].

The DSM-IV criteria for PTSD include:

- Exposure to a significant traumatic event accompanied by an intense, acute emotional response.
- Persistent re-experiencing of the event or aspects of the experience.
- Persistent avoidance of stimuli associated with the event and/or withdrawal from some aspects of life.
- Persistent symptoms of increased arousal.
- The above symptoms must last for more than one month for Acute PTSD and more than three months for Chronic PTSD.

The lifetime prevalence of PTSD in the U.S. general population is between 6% and 10% [6-10], but it is common in other countries as well [11-14]. According to some estimates, PTSD appears to be less prevalent in the general population of Europe at 1.9% [13]. In U.S. military personnel returning from combat in the Iraq war, the incidence of PTSD is as high as 18% [15]. It is estimated that the number of service members returning home with PTSD will ultimately be between 75,000 and 225,000 [16]. In countries with endemic armed conflict, the incidence of PTSD in civilians is often far greater [14, 17, 18].

Although presently we are not aware of any national surveys of lifetime PTSD prevalence in Canada, it is likely that the percentage of Canadians experiencing PTSD is similar to the 8% to 11% listed in samples from the United States and Europe. Likewise, a large prospective, longitudinal epidemiological study of adolescents and young adults in Germany showed a lifetime prevalence of PTSD, including sub-threshold cases, at baseline of 5.6%; by the end of the follow-up period (35-50 months) this had increased

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Halpern 2008)

Benjamin Shechet 7/18/13 12:55 PM  
**Formatted:** Bullets and Numbering

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . . .  
This proposed Canadian pilot study will be the first study of the therapeutic potential of MDMA to be conducted in Canada. In this study, eight of 12 people will receive a dose of MDMA expected to be fully therapeutic (experimental dose) and four of 12 will receive threshold "active placebo" dose of MDMA during three sessions scheduled three to five weeks apart. PTSD symptoms will be assessed at baseline on entry to the study and six weeks after the third double-blind MDMA-assisted psychotherapy session. Cognitive function will also be assessed ... [3]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Freudenmann et al. 2006; Shulgin 1986)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . In the United States, MDMA was used as an adjunct to psychotherapy by a considera ... [4]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Greer and Tolbert 1986; Saunders 1993; Stolaroff 2004)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . Placement in Schedule I prohibited it for use except in a federally-approved research ... [5]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Adamson 1985; d'Otalora 2004; Greer and Tolbert 1998; Metzner and Adamson 2001)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . Case reports and narrative accounts of MDMA-assisted therapy suggest that the treat ... [6]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Greer and Tolbert 1998)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . Some investigators suggest that MDMA be categorized as part of a new class ... [7]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Nichols and Oberlander 1990)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . The term refers to MDMA and similar substances that produce increased sensitivity ... [8]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Baggott et al. 2000; Cole et al. 2002)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . There is evidence that the use of frequent, high doses of Ecstasy in uncontrolle ... [9]

to 10.3% [19]. A survey of 3062 women in Ontario reported a 10.7% lifetime prevalence rate [20]. A study of Canadian peacekeepers reported higher rates of prevalence, with peacekeepers with single deployment diagnosed with PTSD at a rate of 10.9% and a 14.8% rate in peacekeepers that were deployed more than once [21]. These findings suggest that Canadians have PTSD at rates comparable to the US and Europe and that as expected, certain populations will experience higher rates of PTSD.

PTSD is clearly a serious public health problem and contributes substantially to healthcare costs [5, 8, 9]. PTSD is typically a chronic illness [6, 22], associated with high rates of psychiatric and medical comorbidity, disability, suffering, and suicide [7-10, 23]. People suffering from PTSD face challenges in relationships and work productivity [24]. Despite the sheer number of individuals suffering from PTSD and its devastating effects, questions remain concerning the best possible treatments [25]. Two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, which are known to affect the serotonergic components of PTSD, are currently marketed as PTSD medications in the U.S. [26, 27]. SSRIs must be used every day in order to be effective for PTSD symptoms [28]. However, SSRIs are associated with a high rate of discontinuation due to lack of tolerability caused by treatment-emergent side effects that may be under-reported [29, 30].

A wider array of effective treatments are needed for PTSD. At least a third of PTSD patients fail to respond to established PTSD psychotherapies or do not respond in a clinically significant manner [31-33]. In the U.S. National Comorbidity Study, the median time to remission for PTSD was 36 months with treatment and 64 months without treatment. In both subgroups, more than a third of the patients still had symptoms several times per week after 10 years [34]. Forty to 60% of PTSD patients were found to be resistant to treatment in this study. In a comparison of two types of psychotherapy for women with PTSD after sexual assault in 2002, 47% of each treatment group still satisfied diagnostic criteria for PTSD based on Clinician Administered PTSD Scale (CAPS) scores, an outcome which was considered highly efficacious [35]. At least one study of paroxetine indicated that men with PTSD did not respond to this drug [26] and another randomized, double-blind study found no difference between sertraline and placebo in the treatment of PTSD [36]. These findings suggest that there is still a substantial need for innovative treatments for PTSD.

Another treatment approach is to develop drugs and/or psychotherapeutic treatments that may indirectly decrease or eliminate the neurochemical pathologies underlying the chronic hyperarousal associated with PTSD. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies [37-39]. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proven to be effective in treating some symptoms of PTSD [40, 41], although some patients may need more than one type of treatment to reduce or resolve those symptoms [28]. A recent meta-analysis concluded that all "bona fide" psychotherapies, including those listed above, are similarly effective with PTSD [42]. In recent years, there has been a growing amount of research into drugs and other methods that may augment the effectiveness of

- Field Code Changed ... [10]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Kessler et al. 1995)... as report ... [11]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Montgomery and Bech 2000)... [12]
- Unknown
- Field Code Changed ... [13]
- Unknown
- Field Code Changed ... [14]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Brady et al. 2000)... An array of ... [15]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Foa et al. 1999; Resick and Sch ... [16]
- Unknown
- Field Code Changed ... [17]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Brady et al. 2000)... These find ... [18]
- Unknown
- Field Code Changed ... [19]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Frise et al. 2002)... A study of ... [20]
- Unknown
- Field Code Changed ... [21]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Richardson et al. 2007)... Thes ... [22]
- Unknown
- Field Code Changed ... [23]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (2005)... The search for novel an ... [24]
- Unknown
- Field Code Changed ... [25]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Kessler et al. 1995)... Generall ... [26]
- Unknown
- Field Code Changed ... [27]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Resick et al. 2002)... and anoth ... [28]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Foa et al. 1999)... [29]
- Unknown
- Field Code Changed ... [30]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Ursano et al. 2004)... Some pe ... [31]
- Unknown
- Field Code Changed ... [32]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Hamner et al. 2004)... Howeve ... [33]
- Unknown
- Field Code Changed ... [34]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Benish et al. 2008)... [35]
- Unknown
- Field Code Changed ... [36]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Greer and Tolbert 1998; Metzne ... [37]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Nibuya et al. 1996)... Another ... [38]
- Unknown
- Field Code Changed ... [39]
- Berra Yazar 7/18/13 11:43 AM
- Deleted: (Gamma et al. 2000)... This act ... [40]
- Unknown
- Field Code Changed ... [41]
- Berra Yazar 7/18/13 11:43 AM
- ... [42]
- Unknown
- Field Code Changed ... [43]
- Berra Yazar 7/18/13 11:43 AM

psychotherapy for PTSD (see [43] for a review). Examples of this are virtual reality-assisted exposure therapy [44-47] and D-cycloserine-assisted psychotherapy [48]. MDMA-assisted psychotherapy is another such approach.

### 3.2 MDMA

MDMA is a ring-substituted phenylisopropylamine derivative. Chemists at the Merck pharmaceutical company first synthesized it in 1912 [49, 50], though its clinical effects were not subject to formal investigation until the 1980s. MDMA is a potent monoamine releaser that has its greatest effects on serotonin, followed by norepinephrine and dopamine [51-56].

MDMA acutely decreases activity in the left amygdala [57], a brain region involved in interpretation of negative cues, and attenuates amygdalar response to angry faces [58]. This action of MDMA is compatible with its reported reduction in fear of emotional injury or defensiveness [59]. Brain imaging after MDMA indicates less reactivity to angry facial expressions and greater reward in happy faces [58]. A recent study in healthy volunteers found correlations between oxytocin (OT) levels, amygdalar volume, and extraverted personality [60].

OT is a neuropeptide associated with pair bonding and social affiliation in mammals that also attenuates amygdalar response to anxiogenic stimuli [61, 62]. OT administration is associated with increased interpersonal trust and changes in social perception, including attenuated reactivity to threatening faces [63-66]. MDMA elevates OT in peripheral blood [67-69], which is an imperfect but somewhat reliable indicator of elevated OT in the brain [62]. Findings of an association between elevated OT and detectable MDMA in peripheral blood were first reported in a naturalistic study of London nightclub attendees with and without detectable serum MDMA levels [67]. Dumont and colleagues reproduced these results in humans and found that MDMA significantly elevated peripheral plasma OT levels in a placebo-controlled study in healthy volunteers [68], in addition to a positive association between elevated levels of OT and prosocial feelings. Hysek and colleagues replicated these results and reported that administering a serotonin reuptake inhibitor, but not a norepinephrine uptake inhibitor nor several adrenergic antagonists, attenuated the effects of MDMA on OT levels, suggesting a serotonergic mechanism in producing elevated OT [69]. The effects of MDMA on OT may influence empathy or compassion for self and others, decrease defensiveness, and strengthen therapeutic alliance. The multi-level effects of MDMA on monoaminergic signaling and OT, combined with a therapeutic setting, are more likely to provide the opportunity for a corrective emotional experience than OT alone, and could be useful in the treatment of PTSD.

### 3.3 Previous Clinical Experience with MDMA

Classification as a Schedule I drug in the United States has hampered research into the medical uses of MDMA. In recent years, clinical investigation of the safety and efficacy of MDMA-assisted psychotherapy has become more feasible due to an open IND with

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Downing 1986; Greer and Tolbert 1986)... and anecdotal reports ... [44]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Adamson 1985; Widmer 1998)... These include stimulant-like effects and hallucinogen-like effects. Though to date, no controlled study has confirmed acute changes in feelings of closeness to others or empathy, this effect may be reflected in increased sociability or friendliness (Tancer et al. 2003) and has been informally noted in at least one publication ... [45]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Vollenweider et al. 1998)...  
 There has been no evidence of significant or lasting toxicity in subjects participating in Phase I studies of MDMA. This is noteworthy because animal studies have indicated a possibility of long-term serotonergic brain changes after high dose MDMA regimens ... [46]

Unknown  
**Field Code Changed**

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (e. g. Hatzidimitriou et al. 1999; ... [47]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Holland 2001; Rosenbaum and ... [48]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** [5, 29-31]... Treatment wi ... [49]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Rosendorff et al. 2007)... pe ... [50]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Cami et al. 2000a; Freedman et ... [51]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Grob 2001; Harris et al. 2002)... [52]

Unknown  
**Field Code Changed**

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Blake et al. 1990; Nagy et al. 19 ... [53]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Foa et al. 1997; Foa et al. 1993) ... [54]

the FDA [70]. The first double-blind, placebo-controlled U.S. Phase 1 study sanctioned by the FDA was conducted at Harbor-UCLA Medical Center in 1994, with findings that suggested MDMA may cause a statistically significant increase in body temperature, heart rate, and blood pressure in some healthy volunteers [71]. However, these increases were found to be transient and generally tolerable in a controlled clinical setting. Subsequent trials confirmed that MDMA produced significant increases in heart rate and blood pressure that were likely to be well tolerated by healthy individuals [68, 71-76]. The elevation in body temperature noted in healthy volunteers was not clinically significant in sponsor-supported studies at normal ambient temperatures [1, 77]. As of May 2013, MDMA has been administered to more than 845 research subjects, in both Phase 1 and Phase 2 studies, and the sponsor has not been informed of or seen published reports of any unexpected MDMA-related Serious Adverse Events (SAEs) in research studies [1, 51, 54, 58, 59, 68, 69, 71, 72, 74, 76-108].

The potentially therapeutic effects of MDMA were initially investigated in a dose response pilot study funded by MAPS in Spain, in six female survivors of sexual assault with treatment-resistant PTSD [78, 109]. In this study, doses ranging from 50 mg to 75 mg demonstrated mild signs of improvement without any adverse events (AEs) or signs of deteriorating mental health [109].

MAPS sponsored the first U.S. Phase 2 randomized, placebo-controlled study of MDMA-assisted psychotherapy for the treatment of chronic, treatment resistant PTSD, designated as MP-1. MP-1 demonstrated promising results in a sample of 20 subjects [77]. This study employed the CAPS as a primary outcome measure, with PTSD symptoms measured by a blinded Independent Rater (IR) at baseline, three to five days after each experimental session, and at two-month follow-up. Data from this randomized, placebo-controlled pilot study suggests that MDMA is associated with significantly greater improvement in PTSD than placebo (N=20) [77]. Two months after treatment with MDMA-assisted psychotherapy, 83.3% (8 of 12) of the subjects no longer had a PTSD diagnosis and exhibited a 68% drop in CAPS global severity scores. Twenty five percent (two of eight) of the subjects in the placebo and psychotherapy group no longer had a PTSD diagnosis and exhibited a 26% drop in CAPS global severity scores. Seven of the eight subjects receiving placebo went through the treatment program again to receive full dose MDMA. The crossover subjects experienced a 48% drop in CAPS scores and none of these subjects qualified for a PTSD diagnosis at the end of the study, establishing that subjects receiving placebo were not more resistant to treatment. Evaluation of subjects on an average of 45.4 months after receiving MDMA-assisted psychotherapy indicates that the therapeutic benefits have been sustained over time on average, although two subjects experienced a relapse in PTSD symptoms [3]. PTSD symptom severity in subjects who completed the CAPS at long-term follow-up (mean CAPS scores 23.7±22.8, N=16) were statistically equivalent on average to the end of the treatment program (mean CAPS scores 24.6±18.6, N=16) [3].

The sponsor also supported a randomized, double-blind pilot study in 12 subjects with chronic, treatment-resistant PTSD in Switzerland with three experimental sessions,

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Beck and Steer 1984; Beck and Ward 1961)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** that will serve as a measure of depression. It takes five to ten minutes to complete. Participants will complete the BDI at the same times when the CAPS is administered.

The ASIQ is 25-item self-report measure of suicidal ideation and behavior

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Reynolds 1991)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** will be employed along with a face to face interview to assess suicide risk at screening and after completing integrative psychotherapy on the day after an experimental or open-label MDMA-assisted psychotherapy session. The scale produces a single unitary score and has been used to pre... [55]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Osman et al. 1999)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** ... [56]

Unknown  
**Field Code Changed**

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Randolph 1998)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** and the Paced Auditory Serial A... [57]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Roman et al. 1991)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** will all be administered at these ... [58]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Newman et al. 2001)

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . Participants will complete this r... [59]

Unknown  
**Field Code Changed**

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** (Bonny and Savary 1990; Grof 2... [60]

Berra Yazar 7/18/13 11:43 AM  
**Deleted:** . After the first hour, if the partic... [61]

designated as MP-2. The study results suggested a trend toward significant improvement in subjects receiving full dose MDMA, when compared to a 25 mg active placebo MDMA at two-month follow-up [1]. The improvement continued to increase during the 12-month follow-up [1].

In addition, the sponsor supported an initial pilot study with two experimental sessions comparing full dose to 25 mg active placebo MDMA in Israel that enrolled five subjects, with no drug-related Serious Adverse Events (SAEs).

Overall, the results of these studies suggest that MDMA-assisted psychotherapy may be safe and effective in these subjects regardless of trauma etiology.

### **3.4 MDMA-assisted Psychotherapy for PTSD**

MDMA-assisted psychotherapy is an innovative mode of treatment that combines therapeutic techniques with the administration of MDMA, a pharmacological adjunct that may enhance or amplify certain aspects of therapy. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to therapy. MDMA is capable of inducing unique psychopharmacological effects, including:

- Decreased feelings of fear.
- Increased feelings of wellbeing.
- Increased sociability and extroversion.
- Increased interpersonal trust.
- Alert state of consciousness.

Early observers noted increased acceptance of self and others, increased tolerance of emotionally upsetting materials, and the ability to address these issues without extreme disorientation or ego loss [110-113]. In the U.S., MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and other therapists in the treatment of neuroses, relationship problems, and PTSD [110, 111, 114, 115] before it was placed in Schedule I in 1985, as a result of extensive non-medical use [59, 113, 116]. Placement in Schedule I prohibited it for use, except in a federally approved research setting in the U.S.

In contrast to daily administrations of SSRIs, MDMA-assisted psychotherapy consists of several drug-assisted sessions interspersed with a moderate course of non-drug psychotherapy. Thus the effects of MDMA are distinct from and go well beyond those of anti-anxiety drugs such as benzodiazepines. Furthermore, there is no evidence that MDMA creates a physical dependency, as benzodiazepines do. Previous studies of polydrug users have found a small percentage of people exhibit problematic use of Ecstasy (material represented as containing MDMA) [117, 118]. Studies of regular or problematic Ecstasy users indicate that on average, regular use occurs no more often than once a week [119]. Hence, MDMA may have moderate abuse potential. See the Investigator's Brochure (IB) for a more detailed explanation.

Many psychotherapies for PTSD involve the induction and extinction of abnormal autonomic responses through revisiting traumatic experiences in psychotherapy with an appropriate level of emotional engagement [5]. To be effective, exposure must be accompanied by a degree of emotional engagement or “fear activation” while avoiding dissociation or overwhelming emotion [120]. This has been referred to as working within the “optimal arousal zone” or “window of tolerance” [121-123]. When given in an appropriate setting, MDMA produces increased positive mood, facilitates recall and imagination, changes in emotion perception, and social affiliation [58, 68, 69, 103, 124]. These effects are thought to permit revisiting of trauma-associated memories, thoughts, and feelings while maintaining the window of tolerance.

In the context of psychotherapy, MDMA has been noted to reduce defenses and fear of emotional injury while enhancing communication and capacity for introspection [59]. MDMA-assisted psychotherapy is an innovative mode of treatment that combines psychotherapeutic techniques with the administration of MDMA as a pharmacological adjunct. MDMA possesses unique pharmacological properties that may make it especially well suited to use as an adjunct to psychotherapy in PTSD patients, as it appears to stimulate spontaneous engagement in elements of conventional therapies, such as exposure therapy, psychodynamic therapy, and internal family systems therapy in the therapeutic context. Treatment goals of MDMA-assisted psychotherapy for PTSD include alleviating symptoms, interrupting and counteracting the stress-induced neurobiological abnormalities that may be associated with the condition. The biologic and therapeutic approaches are intended to overlap and reinforce each other.

A combined treatment of MDMA and psychotherapy may be especially useful for treating PTSD because MDMA can attenuate the fear response of a perceived threat to one's emotional integrity and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion [77, 109, 111, 113]. Elimination of these conditioned fear responses can lead to more open and comfortable communication about past traumatic events and greater access to information about them [110]. Subjects are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. MDMA seems to engender internal awareness that even painful feelings that arise are an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of the trauma as a past event, a more accurate perspective about its significance, and a heightened awareness of the support and safety that exists in the present. As a result, MDMA-assisted psychotherapy may enable the subjects to restructure their perspective and develop a wider behavioral and emotional repertoire with which to respond to anxiogenic stimuli.

Based on these data and on an extensive review of the MDMA literature, we conclude that MDMA-assisted psychotherapy may have the potential to serve as an innovative treatment for PTSD, particularly in people who fail to respond to currently available therapies, and that the modest risks of administering MDMA within a therapeutic context are outweighed by the possibility that this treatment may offer significant

benefits. A comprehensive review of MDMA research is included in the IB supplied by the sponsor. This document should be reviewed prior to initiating the protocol.

### **3.5 Purpose**

This Phase 2 pilot study is a randomized, double-blind, dose comparison study in 12 subjects that will estimate the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 will consist of two blinded experimental sessions and one open-label experimental session of manualized MDMA-assisted psychotherapy, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. The study will be unblinded one month after the second experimental session in Stage 1, after completion of outcome measures, which constitutes the primary endpoint assessment.

After unblinding, full dose subjects will continue in Stage 1 and receive a third MDMA-assisted psychotherapy session. The benefit of three vs. two full dose sessions will be assessed. Subjects who received the comparator dose during Stage 1 will have the opportunity to cross over to Stage 2 with three experimental sessions. Stage 2 will be used to explore the optimal therapeutic dose of MDMA using a clinical titration dosing strategy.

A blinded Independent Rater will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session and at equivalent time points in Stage 2. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2.

A therapy team will conduct psychotherapy visits according the treatment manual provided. The team will include two licensed therapists who will work together as co-therapists.

### **4.0 Ethics**

The trial will not be initiated until appropriate Health Canada and Institutional Review Board (IRB) approval of the protocol and the informed consent document has been obtained. All documents will be submitted to other authorities in compliance with local jurisdictions. The IRB and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements. The protocol will also be submitted to FDA under U.S. IND #63,384.

This trial will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonization (ICH) guidelines, and applicable Standard Operating Procedures (SOPs). The trial will be conducted under a protocol reviewed and approved

by an IRB. The trial will be conducted by scientifically and medically qualified persons. The benefits of the study will be considered in proportion to the risks. The rights and welfare of the subjects will be respected. The physicians conducting the trial do not find the hazards to outweigh the potential benefits. Each subject will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

### **5.0 Informed Consent**

The Clinical Investigator is responsible for overseeing informed consent is obtained in adherence to GCP and according to applicable regulations prior to entering the subject into the trial. The informed consent discussion must be conducted by a person who is qualified according to regulations. Written information about the trial will be provided in an understandable Informed Consent Form (ICF). Written consent must be given by the subject. The ICF document must be explained and the subjects' questions must be answered. The subject should have the opportunity to inquire about details of the MDMA-assisted session and to consider participation.

The ICF will state the probability of random assignment to the full dose group or the comparator dose group, however there will be a level of obfuscation, which makes it unclear that there is only one comparator dose of MDMA. The ICF will indicate the comparator dose may or may not contain MDMA. If subjects ask about the composition of investigational product in the comparator dose group, the exact contents of the comparator dose will be said to include lactose and may or may not include MDMA, however everyone assigned to the comparator dose group will have the opportunity to receive active dose MDMA during Stage 2. For all subjects in the comparator dose group, the content of the comparator dose will be disclosed after the primary endpoint visit when unblinding occurs. Unblinding and debriefing at the primary endpoint will take place with the co-therapist team and the subject. During the debriefing, subjects will be informed of the contents of the investigational product they received during the blinded experimental sessions in Stage 1.

In addition to the explanation of study visits, the ICF should include that access to original medical records and processing of coded personal information must be authorized. Written consent to take part in the study includes giving the Clinical Investigators permission to view the subject's recent medical records to assess protocol eligibility, if needed. Information necessary for protocol participation includes past medical history, psychiatric interview, physical examination, and clinical laboratory tests.

Eligible subjects may only be included in the study after signing the IRB approved ICF. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol, including screening activities). The process of obtaining informed consent should be documented in the subject source records. The therapists will provide a copy of the signed ICF to the subject and will maintain the original in the ISF.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised ICF and written information should receive approval from an IRB before use. The subject should be informed in a timely manner if new information becomes available that might affect the decision to take part in the MDMA-assisted session. The communication of this information should be documented.

Subjects can withdraw consent at any time without prejudice. If a subject withdraws consent but does not revoke Health Information Protection Act (HIPA), the Clinical Investigators will have access to the subject's study related medical records and data will be used. If a subject revokes consent and HIPA, the Clinical Investigators will have access to the subject's medical records prior to the date and time of revocation but the data will not be used.

## **6.0 Study Objectives**

The overall objective of this study is to examine whether the full dose of MDMA versus the comparator dose of MDMA used in conjunction with manualized psychotherapy will reduce or attenuate PTSD symptoms as evaluated by standard clinical measures and to collect safety data.

### **6.1 Primary Objective**

- Assess changes in PTSD symptoms in subjects receiving the full dose of MDMA compared to the comparator dose as measured by Global CAPS scores at baseline and the primary endpoint, one month after the second experimental session.

### **6.2 Secondary Objectives**

The following objectives will compare full dose subjects to comparator dose subjects in Stage 1:

- Assess changes in self-reported PTSD symptoms as measured with the PTSD Diagnostic Scale (PDS) at baseline, after each experimental session and/or the primary endpoint.
- Assess depression symptoms with the Beck Depression Inventory (BDI-II) at baseline and the primary endpoint.
- Assess global functioning with the Global Assessment of Functioning (GAF) at baseline and the primary endpoint.
- Assess changes in personality with the Neuroticism Extroversion Openness Personality Inventory (NEO-PI) at baseline and the primary endpoint.
- Assess self-reported sleep quality with the Pittsburgh Sleep Quality Index (PSQI) at baseline and the primary endpoint.
- Assess self-reported dissociation symptoms with the Dissociation Experiences Scale II (DES-II) at baseline and the primary endpoint.

- Assess self-reported posttraumatic growth with the Posttraumatic Growth Inventory (PTGI) at baseline and the primary endpoint.

The following objectives will compare effects in specified subjects:

- Assess PTSD symptoms via CAPS and PDS, depression symptoms via BDI-II, global functioning via GAF, sleep quality via PSQI, posttraumatic growth via PTGI, changes in personality via NEO-PI and dissociation symptoms via the DES-II, throughout Stage 2 in comparison to Stage 1 in crossover subjects.
- Assess long-term effects of MDMA-assisted psychotherapy on symptoms of PTSD, depression, global function, sleep quality, posttraumatic growth, and dissociation symptoms via CAPS, PDS, BDI-II, GAF, PTGI, PSQI, PTGI (in reference to start of the study), DES-II, and changes in personality via NEO-PI one year after the final experimental session for each subject.

The following objectives will include exploratory analyses intended to inform protocol design:

- Explore the effects of each experimental session upon self-reported changes in consciousness, as those associated with a transformational or mystical experience via the States of Consciousness Questionnaire (SOCQ).
- Assess the effect of the third experimental session for full dose subjects in Stage 1 and Stage 2 using CAPS, PDS, BDI-II, GAF, PSQI, PTGI, NEO-PI, and DES-II.
- Assess the ability of the Clinical Investigators and subjects to accurately guess condition assignment in Stage 1.
- Correlate adherence to the treatment manual with Global CAPS scores using adherence criteria ratings to assess videos of psychotherapy sessions.

### **6.3 Safety Objectives**

The study will monitor and ensure safety in subjects enrolled in the study by assessing physiological effects, psychological distress, spontaneously reported reactions, and suicidality.

- Vital signs (blood pressure, heart rate, and temperature) and Subjective Units of Distress (SUD) will be measured during each experimental session. Comparisons will be made for SUD scores and vital signs between each condition.
- SAEs, AEs, and spontaneously reported reactions will be collected during the study according to protocol Section 14.0.
- Suicidality will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS) during visits prior to and after experimental sessions, twice during experimental sessions, and several times after each experimental session. Comparisons will be made for C-SSRS scores for subjects in each condition. The same schedule of assessment will be followed during Stage 2.

- Assess cognitive function with the Paced Auditory Serial Addition Test (PASAT) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and the primary endpoint by condition, and end of Stage 1/end of Stage 2 for maximal exposure.
- Collect changes to pre-existing tinnitus and/or chronic pain symptoms using a visual analog scale, specifically in subjects with a medical history of tinnitus and/or chronic pain.

## **7.0 General Investigational Plan**

### **7.1 Recruitment and Subject Population**

Subjects may be men or women aged 21 or older with a confirmed diagnosis of chronic, treatment-resistant PTSD who have undergone psychotherapeutic or psychopharmacological treatment for PTSD of adequate dose/duration without achieving remission. Subjects who discontinued PTSD treatment due to inability to tolerate psychotherapy (e.g. due to persistent "over-engagement") or psychopharmacology due to treatment-emergent side effects would not be excluded. Subjects will also not be excluded for having more than one traumatic event. Subjects must have a CAPS score equal to or greater than 60 and meet all inclusion criteria and no exclusion criteria at baseline. They must be in good physical health and without major medical disorders that might affect the safety or tolerability of MDMA. Seven of 12 subjects will be randomly assigned to receive the full dose and five subjects will be randomly assigned to receive the comparator dose.

Study subjects will be Canadian residents recruited by letters of referral sent to psychiatrists and psychotherapists, written advertisements, announcements placed on appropriate Internet sites and the sponsor site, and through word of mouth. Site staff will interview prospective subjects by telephone to learn if they meet basic eligibility criteria. If the prospective subject is interested in taking part in the study, the Clinical Investigators will provide the prospective subject with consent materials for review and consideration.

### **7.2 Enrollment Criteria**

#### **7.2.1 Inclusion Criteria**

Individuals eligible to be enrolled into this protocol are subjects who:

1. Meet DSM-IV criteria for current PTSD, with a CAPS score of 60 or higher, indicating moderate to severe PTSD symptoms;
2. Have chronic PTSD, defined as PTSD persisting for longer than 6 months; subjects may have experienced one or more traumatic event;
3. Have treatment-resistant PTSD, who were unable to achieve remission despite receiving adequate dose/duration of psychotherapy or psychopharmacology with an SSRI, mirtazapine, or MAOI, or who discontinued treatment due to either:

- a. Inability to tolerate psychotherapy for PTSD (e.g. persistent “over-engagement” when attempting Prolonged Exposure Therapy).
  - b. Inability to tolerate psychopharmacology for PTSD due to treatment-emergent side effects;
4. Are at least 21 years old;
5. Are willing to commit to medication dosing, experimental sessions, follow-up session and completion of evaluation instruments;
6. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. If the subject is on stimulants for ADHD at baseline, they can continue to use them at the same dose and frequency as long as they discontinue five half-lives before each experimental session and do not restart for ten days after each experimental session. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician;
7. If in ongoing psychotherapy at the time of recruitment, are able to continue to see their outside therapist during the course of the study. Subjects must sign a release permitting the Clinical Investigators to communicate directly with their therapist. Subjects may not change therapists, increase the frequency of therapy, or commence any new type of therapy until after the evaluation session at the end of Stage 1 or Stage 2, as applicable;
8. Agree to refrain from taking, for one week preceding each experimental session:
  - a. Any herbal supplement (except with prior approval of the research team).
  - b. Any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team).
  - c. Any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team).  
Note: Must have physician’s approval;
9. Agree to take nothing by mouth except alcohol-free liquids after midnight the evening before the experimental session. Subjects must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each experimental session;
10. Are willing to remain overnight at the clinic after each experimental session until the integrative session occurring the next morning. An attendant with previous training in managing psychological distress will be present to assist with personal needs if requested and offer dinner and breakfast;
11. Are willing to locate an individual to drive them home the morning after the experimental sessions, after the integrative session. If a subject is unable to locate someone to transport them home, the Clinical Investigators will assist the subject in obtaining transport from the clinic to the subject’s home or any other location where he or she is staying temporarily;
12. Are willing to be contacted via telephone on a daily basis by one of the Clinical Investigators for a week after each experimental session;

13. Are willing to provide a contact (relative, spouse, close friend, or other caregiver) who is willing and able to be reached by Clinical Investigators in the event of a subject becoming suicidal;
14. Agree to inform the Clinical Investigators within 48 hours of any planned medical interventions;
15. Have a negative pregnancy test and must agree to use an effective form of birth control, if the participant is a female of childbearing potential;
16. Are literate and proficient in reading documents written in English and speaking English;
17. Agree to have all clinic visit sessions recorded to audio and video;
18. Agree not to participate in any other interventional clinical trial for the duration of this clinical trial, including the follow-up period.

### **7.2.2 Exclusion Criteria**

Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control;
2. Have a history of, or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder;
3. Have dissociative identity disorder or an eating disorder with active purging;
4. Have evidence or history of significant hematological, endocrine, cerebrovascular, cardiovascular, cardiac, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder, or any other medical disorder judged by the Principal Clinical Investigator to significantly increase the risk of MDMA administration (Subjects with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded);
5. Have hypertension using the standard criteria of the American Heart Association of values of 140/90 or higher assessed on three separate occasions, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia;
6. Weigh less than 48 kg;
7. Have used "Ecstasy" (illicit drug preparations purported to contain MDMA) more than five times in the last 10 years or at least once within six months of enrollment;
8. Would present a serious suicide risk, or who are likely to require hospitalization during the course of the study, as determined through psychiatric interview, responses to C-SSRS and through clinical judgment of the Principal Clinical Investigator;
9. Require ongoing concomitant therapy with a psychiatric drug, including but not limited to SSRIs, SNRIs, or MAOIs;
10. Meet DSM-IV criteria for active substance abuse or dependence for any substance other than caffeine or nicotine in the past 6 months;
11. Are not able to give adequate informed consent;

12. Have any current problem, which in the opinion of the Principal Clinical Investigator or Medical Monitor, might interfere with participation in the study.

### **7.3 Planned Duration of Study and Visit Windows**

Subjects enrolled in this study will fall into two categories that will determine the duration of the study. These include the follow-up portion of the study, which encompasses 12 months after the final experimental session.

- Full dose subjects completing Stage 1 only: 15 months
- Comparator dose subjects who complete Stage 2: 18 months

Screening may take up to two months, with the baseline CAPS being conducted no more than 8 weeks before the first experimental session, leaving room for appropriate medication washout of at least 5 half-lives of pre-study psychiatric medications and active metabolites, and one additional week for stabilization. For example, the maximum washout would be 7 weeks for subjects tapering off of fluoxetine plus one week for stabilization. Preparatory sessions should be scheduled approximately one week apart, with the first experimental session taking place 3-5 weeks after enrollment, and at most 8 weeks after the baseline CAPS. The maximum window from the start of screening to the first experimental session is 13 weeks. The optimal timing for Stage 2 is one month after the primary endpoint visit in Stage 1, with a maximum allowable window of five months. Any delay between visits would result in a corresponding extension of study duration.

### **8.0 Drug Description and Dosage**

Subjects assigned to the full dose condition will receive three experimental sessions with an initial dose of 125 mg possibly followed 1.5 to 2.5 hours later by an optional supplemental dose of 62.5 mg MDMA. Subjects in the comparator dose condition will be assigned to receive two experimental sessions with an initial dose of 50 mg MDMA possibly followed 1.5 to 2.5 hours later by an optional supplemental dose of 25 mg MDMA. Seven of 12 subjects, or 58%, will be assigned to the full dose condition, and five of 12, or 42%, will be assigned to the comparator dose condition.

Subjects in the comparator dose condition during Stage 1 will have the opportunity to cross over to Stage 2. Stage 2 will be used to explore the optimal therapeutic dose using a clinical titration dosing strategy using varied active doses of MDMA. In Stage 2 subjects will receive an initial dose of 100 mg followed 1.5 to 2.5 hours later by an optional supplemental dose of 50 mg MDMA during the first experimental session. In the second and third session they will receive an initial dose of 100 mg or 125 mg MDMA followed 1.5 to 2.5 hours later by an optional supplemental dose of 50 mg or 62.5mg as appropriate to the initial dose of MDMA. The decision to titrate the dose in the second and third session will be based on the experience of the first session, if 100mg MDMA does not seem to be the optimal therapeutic dose based on the first experimental session in Stage 2, the dosage may be increased by an increment of 25mg

in order to achieve the optimal therapeutic dose. The supplemental doses for each experimental session will be half of the initial dose, respectively.

The initial and supplemental doses of 125 mg MDMA and 62.5 mg used in the full dose condition are identical to those in use in other sponsor-supported studies of MDMA-assisted psychotherapy. Previous researchers have also used doses within this range [71, 72, 74, 75, 124, 125]. Doses equal to or exceeding 125 mg have been employed in previous uncontrolled and controlled studies of MDMA [74, 75, 91, 126-128]. Prior to the time MDMA was placed in Schedule I in the U.S., identical or similar doses and regimens were used in psychotherapy [59, 111, 113]. The initial full dose is expected to produce all the common effects of MDMA, including changes in affect (mood) and cognition and changes in feelings of interpersonal closeness and trust. The supplemental dose will prolong subjective drug effects without producing physiological effects any greater than peak effects occurring after the initial dose. In this study, the 100mg MDMA initial dose will be administered in the first experimental session in Stage 2. The co-therapists, in consultation with the subject, will have the option to explore whether this dose or the clinical titration of an additional 25mg initial dose, with corresponding supplemental doses, would constitute the optimal therapeutic dose for the second and/or third experimental sessions.

The doses to be compared in this study have been chosen on the basis of the Sponsor's ongoing initiative to develop a dose response curve of MDMA-assisted psychotherapy in the treatment of PTSD. The Stage 1 comparator dose of 50 mg to 75 mg MDMA may reduce anxiety or improve access to emotionally upsetting material, in addition to producing slight alterations in consciousness, such as increased relaxation or tension [72, 109, 129]. The goal of this study is to estimate the effect size of comparator and full dose MDMA given that the comparator dose may have some level of efficacy.

**Table 1. Stage 1 Drug Doses**

<b>Experimental Session</b>	<b>Dose</b>	<b>Initial Dose</b>	<b>Optional Supplemental Dose</b>	<b>Min-Max Cumulative Dose</b>
1 and 2	Comparator Dose	50 mg	25 mg	50-75 mg
1, 2, and 3	Full Dose	125 mg	62.5 mg	125-187.5 mg

**Table 2. Stage 2 Drug Doses**

<b>Experimental Session</b>	<b>Dose</b>	<b>Initial Dose</b>	<b>Optional Supplemental Dose</b>	<b>Min-Max Cumulative Dose</b>	<b>Min-Max Cumulative Dose with Titration</b>
1	Active Dose	100 mg	50 mg	100-150 mg	
2 and 3	Active Dose	100 mg	50 mg	100-150 mg	
	+ Optional Titration Dose	25 mg	12.5 mg		125-187.5 mg

### **8.1 MDMA Compounding, Doses, and Labeling**

The investigational product (IP) for the study is MDMA. Bulk IP will be received at the pharmacy via a secure delivery system in accordance with all local regulations. A receipt will be kept on file at the pharmacy and at the site. Six strengths of IP will be created: 125 mg, 100 mg, 62.5 mg, 50 mg, 25 mg and 12.5 mg. Each of these batches will be created with the bulk MDMA and varied amounts of lactose during the compounding process. A "packing stat" will be created by filling 10 capsules with lactose to calibrate the amount of compounded IP per capsule. Once encapsulated, the total number of capsules will be recorded on the drug accountability log.

The encapsulation will be performed by a pharmacist who has the appropriate skills. The MDMA will be weighed out (calculated as the weight of the hydrochloride salt) into gelatin capsules in combination with lactose used to ensure that all capsules have similar weights. Capsules for all experimental, double-blind sessions will be prepared in such a way as to prevent Clinical Investigators and subjects from distinguishing contents of full dose and comparator dose capsules. Dosage for open-label sessions will be clearly indicated in the packaging.

The IP for each experimental session will be packaged in one primary container, labeled with a unique container number, protocol number, drug name, lot number, sponsor name, experimental session number, stage, and a statement that the drug is restricted to clinical trial use only. All drug labels will comply with local regulations and will be provided in English. The initial and supplemental dose will be packaged in separate labeled "inner envelopes" within the primary container. There will be one primary container per subject per experimental session. The sponsor randomization monitor will oversee the process of blinded drug packaging conducted by the pharmacist according to the randomization list. This list will not be shared with any blinded site or sponsor staff. The pharmacist and randomization monitor will be the only staff who are unblinded.

#### **Figure 1. Examples of Drug Labels**

##### **Holding Box Labels**

Holding Box Label
MAPS Study# MP-4
Investigational Product: MDMA
Dose: XXmg
Lot #: XXX
Restricted drug for clinical trial use by Qualified investigator only

MAPS Study MP-4  
 Canada

Amendment 1 Version 2  
 June 20, 2013

**Stage 1 Primary Container Labels**

Blinded	Open Label Session 3
<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060                      Study # MP-4                      Stage 1 Blinded                      Experimental Session # _____                      Container # XXX                      Lot # XXX                      Expiry date: XXX                      Store at 22°C</p> <p>Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060                      Study # MP-4                      Stage 1 Open Label                      Experimental Session #3                      Container # XXX                      125mg &amp; 62.5mg MDMA                      Lot # XXX                      Expiry date: XXX                      Store at 22°C</p> <p>Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>

**Stage 1 Inner Envelope Labels**

Blinded	Blinded
<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4                      Stage 1                      Container # XXX                      Initial Dose                      Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4                      Stage 1                      Container # XXX                      Supplemental Dose                      Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>
Open Label Session 3	Open Label Session 3
<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4                      Stage 1 Open Label                      Container # XXX                      Initial Dose 125mg MDMA                      Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Inner Envelope</p> <p>MAPS Study # MP-4                      Stage 1 Open Label                      Container # XXX                      Supplemental Dose 62.5mg MDMA                      Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>

**Stage 2 Primary Container Labels**

Open Label	Open Label	Open Label
<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060                      Study # MP-4                      Stage 2                      Experimental Session # 1                      Container # XXX                      100mg &amp; 50mg MDMA                      Lot #: XXX                      Expiry date: XXX                      Store at 22°C</p> <p>Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060                      Study # MP-4                      Stage 2                      Experimental Session # 2                      Container # XXX                      100+25mg &amp; 50+12.5mg MDMA                      Lot #: XXX                      Expiry date: XXX                      Store at 22°C</p> <p>Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>	<p style="text-align: center;">Primary Container</p> <p>MAPS 1215 Mission St, Santa Cruz, CA USA 95060                      Study # MP-4                      Stage 2                      Experimental Session # 3                      Container # XXX                      100+25mg &amp; 50+12.5mg MDMA                      Lot #: XXX                      Expiry date: XXX                      Store at 22°C</p> <p>Subject # _____                      Restricted drug for clinical trial use by Qualified investigator only</p>

## **Stage 2 Inner Envelope Labels**

### **Unblinded Session 1**

Inner Envelope  
MAPS Study # MP-4  
Stage 2 Open Label  
Experimental Session # 1  
Container # XXX  
Initial Dose 100mg MDMA  
Subject # \_\_\_\_\_  
Restricted drug for clinical trial use by  
Qualified investigator only

### **Unblinded Session 1**

Inner Envelope  
MAPS Study # MP-4  
Stage 2 Open Label  
Experimental Session # 1  
Container # XXX  
Supplemental Dose  
50mg MDMA  
Subject # \_\_\_\_\_  
Restricted drug for clinical trial use by  
Qualified investigator only

### **Unblinded Session 2 or 3**

Inner Envelope  
MAPS Study # MP-4  
Stage 2 Open Label  
Experimental Session # \_\_\_\_\_  
Container # XXX  
Initial Dose 100mg MDMA  
Open Label  
Subject # \_\_\_\_\_  
Restricted drug for clinical trial use by  
Qualified investigator only

### **Unblinded Session 2 or 3**

Inner Envelope  
MAPS Study # MP-4  
Stage 2 Open Label  
Experimental Session # \_\_\_\_\_  
Container # XXX  
Initial Dose increment  
25mg MDMA  
Subject # \_\_\_\_\_  
Restricted drug for clinical trial use by  
Qualified investigator only

## **8.2 MDMA Accountability**

Forms will be provided to track drug accountability and administration throughout the study. Blinded drug accountability and administration logs will be reviewed during routine monitoring visits. MDMA will be handled in accordance with all provincial and national regulations and forms pertaining to the use of controlled substances in Canada, and forms will be maintained by the pharmacist.

Each primary container label will contain a unique container number for the drug assigned to a single experimental session. The container numbers will be used to track drug administration in the Source Record and the drug administration log. The web-based randomization system will enable tracking of blinded primary containers for drug accountability purposes.

## **8.3 MDMA Storage and Handling**

MDMA is a Schedule III compound in Canada and the pharmacist will store and handle it in compliance with relevant Federal and Province regulations. The pharmacist will be responsible for storing and dispensing the MDMA in accordance with all regulatory requirements. The IP will be stored at room temperature in a locked safe at the pharmacy and only the pharmacist will have access to it.

IP will only be removed for a single experimental session at a time and will be administered orally at the office of the Principal Clinical Investigator (PI). All doses administered will be recorded on the appropriate accountability and administration logs. Only the initial dose is required to be given at each experimental session. Supplemental doses are provided for each experimental session but are optional to use. In addition, the clinical titration doses with corresponding supplemental dose are provided in Stage 2 session 2 and 3 and are optional to use.

The pharmacist will dispense one primary container with the appropriate container number to the PI before each experimental session. If the PI decides not to administer the optional supplemental dose and/or the optional clinical titration dose in a given experimental session, the unused capsules will be kept in their respective inner envelopes inside of the primary container until the end of the experimental session. At the end of the experimental session, the PI will return the container and any remaining unused capsules to the Pharmacist for return to the pharmacy safe. At the end of the study, the Sponsor will be consulted to determine the course of action if there is any unused IP remaining.

### **9.0 Method**

This Phase 2 pilot study is a randomized, double-blind, dose-response study in 12 subjects comparing the effect size of comparator dose to full dose MDMA as an adjunct to manualized MDMA-assisted psychotherapy. A therapy team will conduct psychotherapy visits according to the treatment manual provided. The team will be two licensed therapists who will work together as co-therapists. Seven subjects will be randomized to the full dose condition and five subjects will be randomized to the comparator dose condition. Stage 1 of the study will consist of two blinded experimental sessions for all subjects and one open-label experimental session for full dose subjects, each lasting six to eight hours and scheduled three to five weeks apart, within a moderate course of non-drug psychotherapy. Each subject will be unblinded after completion of outcome measures at the primary endpoint, one month after the second experimental session in Stage 1. A blinded IR will assess the severity of PTSD symptoms at baseline, at the primary endpoint one month after the second experimental session, two months after the third open-label experimental session as well as the equivalent time points in Stage 2. After unblinding, full dose subjects will have one more full dose session in Stage 1 and comparator dose subjects will have the opportunity to cross over to open-label Stage 2, which will be used to explore the optimal therapeutic dose for cross over subjects. All subjects will complete a long-term follow-up visit 12 months after their final experimental session in either Stage 1 or Stage 2. This study will provide an estimate of effect size based on a dose comparison of PTSD symptoms to MDMA-assisted psychotherapy.

### **9.1 Randomization**

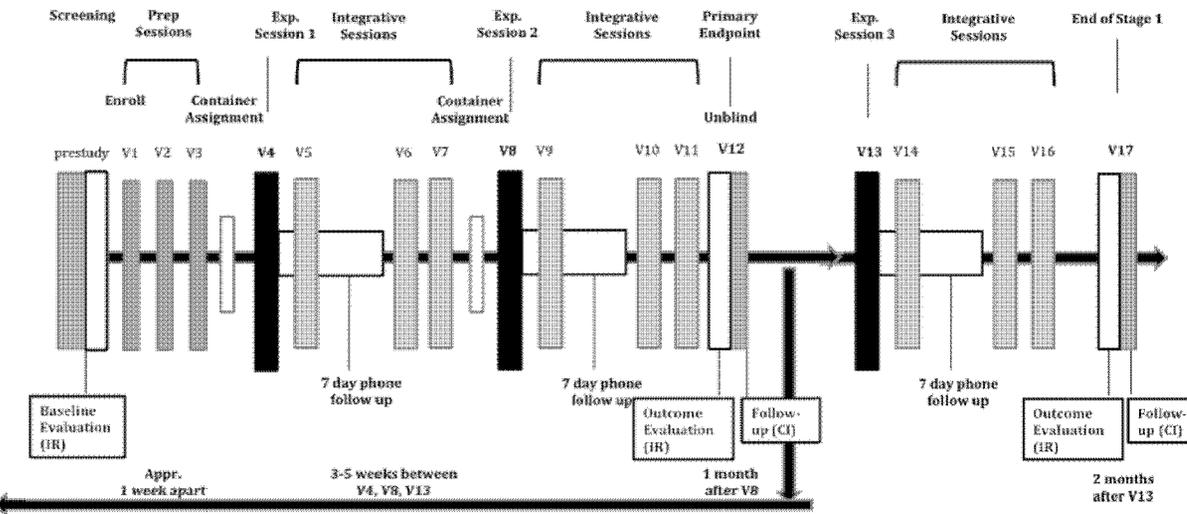
In total, 12 subjects will be enrolled in the study. The randomized portion of the study will be blinded and there will be a 7:5 ratio between subjects in the full dose and comparator dose conditions. An unblinded randomization monitor will generate the randomization list prior to enrollment of subjects. Subjects will be assigned sequential subject numbers upon enrollment for randomization assignment in a blinded fashion. Upon enrollment, the randomization monitor will provide the PI with the randomization enrollment code corresponding to that subject's sequential subject number. A unique container number will be pre-printed on the container labels corresponding to doses for each experimental session. The PI will enter the randomized enrollment code into the web-based randomization program to obtain the container number based on the condition assignment for each blinded experimental session. Blinded personnel will conduct all study evaluations in the randomized portion of the study until the blind is broken for each subject at the primary endpoint per protocol via the web-based randomization program. Detailed instructions will be provided to the site in a separate document.

The therapists, the Independent Rater, and all site personnel except the pharmacist will remain blind to condition assignment. If there is an adverse event or other emergency requiring knowledge of the subject's condition assignment, the blind may be broken for an individual subject by contacting the Sponsor's Randomization Monitor. In most cases it should be sufficient to inform the treating physician for the emergency that the subject had received a minimum of 50mg MDMA and a maximum of 125mg MDMA with a supplemental dose of 62.5mg MDMA.

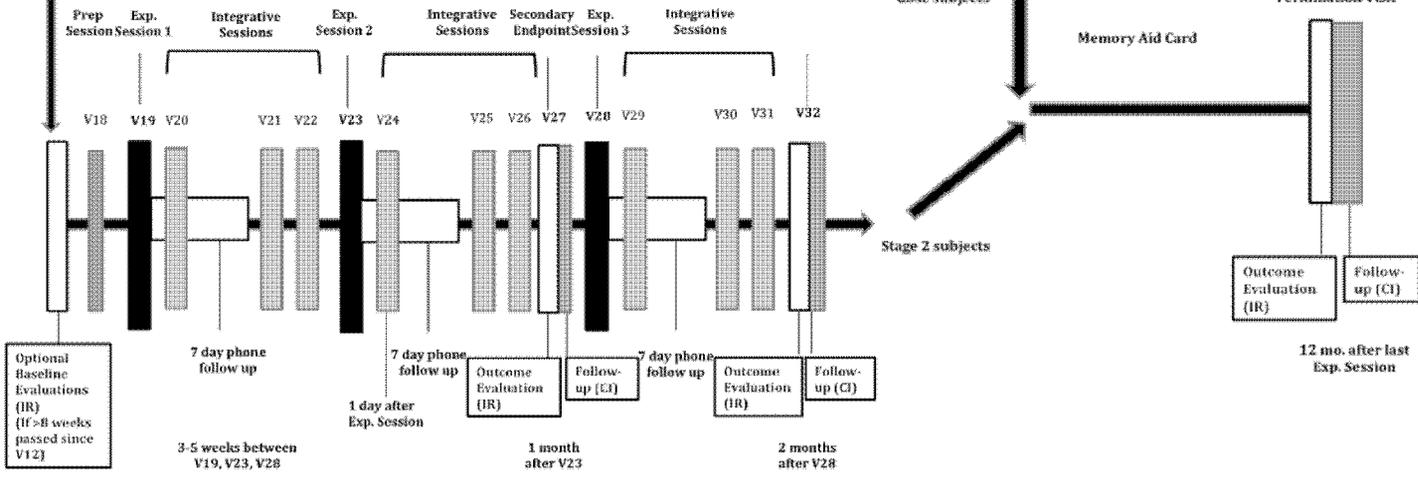
### **9.2 Subject Numbering**

Prior to enrollment, subjects will be tracked with a secondary identifier number and a screening number assigned sequentially starting at "001". Subjects who meet the enrollment criteria will be enrolled in the study and assigned a 5-digit subject number. The first two digits identify the study site. The next three digits identify the subject within the site and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 04001, second 04002, etc.

### Stage 1 Summary of Events



### Stage 2 Summary of Events



**Table 3. Time & Events Stage 1**

Study Phase	Screen/ Baseline	Preparatory Sessions	Experimental Session 1		Experimental Session 2		Primary Endpoint	Experimental Session 3		End of Stage 1
Visit #	Screening/Baseline	V1, V3	V4	V5, V7	V8	V9, V11, V12	V13	V14, V15, V16	V17	
Type of Visit	Screening/Baseline	Preparatory	Experimental	Integrative	Experimental	Integrative	Outcome	Integrative	Outcome	
Visit Timing	Visit 2 monthly prior to V1	1 week apart	1-5 weeks post-baseline	Between V4 and V5	1-5 weeks post V4	Between V8 and V12	1 month post V8	Between V14 and V16	2 months post V16	
Initial Phone Screen	✓									
Informed Consent	✓									
Medical/Psychiatric History	✓									
General Physical Exam, ECG	✓									
Brief Neurological Exam	✓									
SCID-IV (R)	✓									
Clinical Lab Tests with HIV test	✓									
Collect Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Medication Taper (if applicable)		✓								
Study Enrollment (if eligible)		✓								
Record to Audio/Video		✓	✓	✓	✓	✓	✓	✓	✓	
General Wellbeing		✓	✓	✓	✓	✓	✓	✓	✓	
Drug Screen	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Pregnancy Screen (if applicable)	✓									
Obtain Container Assignment			✓ <sup>B</sup>		✓ <sup>B</sup>					
CAPS, GAF, BDI-II, NEO-PI, PSQI	✓						✓		✓ <sup>C</sup>	
PTGI, DES-II	✓								✓	
RRANS/PASAT	✓								✓	
PDS	✓			✓ <sup>A</sup>	✓ <sup>A</sup>	✓ <sup>A</sup>	✓	✓ <sup>A</sup>	✓	
S-SSRS	✓	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓	
Administer Drug + Therapy		✓	✓	✓	✓	✓		✓		
Monitoring of BP, Pulse, and Temp.		✓	✓	✓	✓	✓	✓	✓	✓	
SCID			✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	✓ <sup>H</sup>	
Belief of Condition Assignment			✓	✓	✓	✓	✓	✓	✓	
Overnight Stay, SOCCQ			✓	✓	✓	✓	✓	✓	✓	
Integrative Therapy Session				✓		✓		✓		
7 Days Integrative Telephone Contact				✓		✓		✓		
AEs Requiring Medical Attention			✓	✓	✓	✓	✓	✓	✓	
Serious Reported Reactions & All AEs			✓	✓	✓	✓	✓	✓	✓	
Changes in Tinnitus and/or Pain	✓ <sup>I</sup>		✓ <sup>I</sup>	✓ <sup>I</sup>	✓ <sup>I</sup>	✓ <sup>I</sup>	✓ <sup>I</sup>	✓ <sup>I</sup>	✓ <sup>I</sup>	
AEs of Psychiatric Status or Withdrawal		✓	✓	✓	✓	✓	✓	✓	✓	
Serious Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	
Issue Mynarx Aid Card			✓	✓	✓	✓	✓	✓	✓	
Unblinding							✓		✓	
Perception of Experimental Sessions							✓		✓	
RRPO							✓		✓	

Amy Emerson 6/17/13 9:36 PM  
**Comment:** Add a note that says see section xxx for visit windows???

A... First integrative session is one day after experimental session; B... At least 24 hours prior to experimental session; C... Approximately six hours post MDMA; D... At the beginning of the session; E... As needed; F... Approximately every 60 minutes; G... Given on 2nd preparatory session after washout; H... Only for subjects starting LITRU; I... Every face to face visit and Day 2 and Day 7 phone calls only; J... Reactions collected for seven days post experimental session; K... On the day of the first integrative session following the experimental session; L... One month after the second experimental session but before the third experimental session; M... On the day of the third integrative session; N... After unblinding for full dose subjects only; O... Only on Visit 1; P... Only in subjects with pre-existing tinnitus and/or chronic pain; Q... All measures listed except for the NEO-PI.