MAPS

MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

Clinical Development Plan:
MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder (PTSD)

Prospectus

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The Multidisciplinary Association for Psychedelic Studies (MAPS) is a membership–based, IRS–approved 501(c)(3) non-profit research and educational organization founded in 1986.

Our mission is (1) to treat conditions for which conventional medicines provide limited relief— such as posttraumatic stress disorder (PTSD), pain, drug dependence, and anxiety and depression associated with end-of-life issues— by developing psychedelics and marijuana into prescription medicines; (2) to cure many thousands of people by building a network of clinics where treatments can be provided; and (3) to educate the public honestly about the risks and benefits of psychedelics and marijuana.

MAPS was founded in 1986, one year after the Drug Enforcement Administration (DEA) overruled a DEA Administrative Law Judge (ALJ) recommendation and made MDMA a Schedule I drug, criminalizing both its recreational and therapeutic uses. We pursue our research mission by helping and/or sponsoring scientific researchers to design, obtain governmental approval for, fund, conduct, and report on psychedelic and marijuana research in human volunteers with the goal of developing psychedelics and marijuana into legal prescription medicines.

We are actively developing and funding clinical trials with human subjects in accordance with guidelines set forth by the U.S. Food and Drug Administration, the European Medicines Agency, and the International Council on Harmonization (ICH/GCP). During this process we are training therapists to administer psychedelic drugs in therapeutic settings. We believe that psychedelics and marijuana, when used in proper settings, can be beneficial for such uses as psychotherapeutic treatment, physiological research and treatment, addiction treatment, pain relief, spiritual exploration, creativity research, brain physiology research, and related scientific inquiries.

MAPS operates as

a non-profit pharmaceutical company.

All of the drugs

involved in MAPS' research

will be generic substances

for public benefit.

When these substances

become prescription medicines,

MAPS will not have

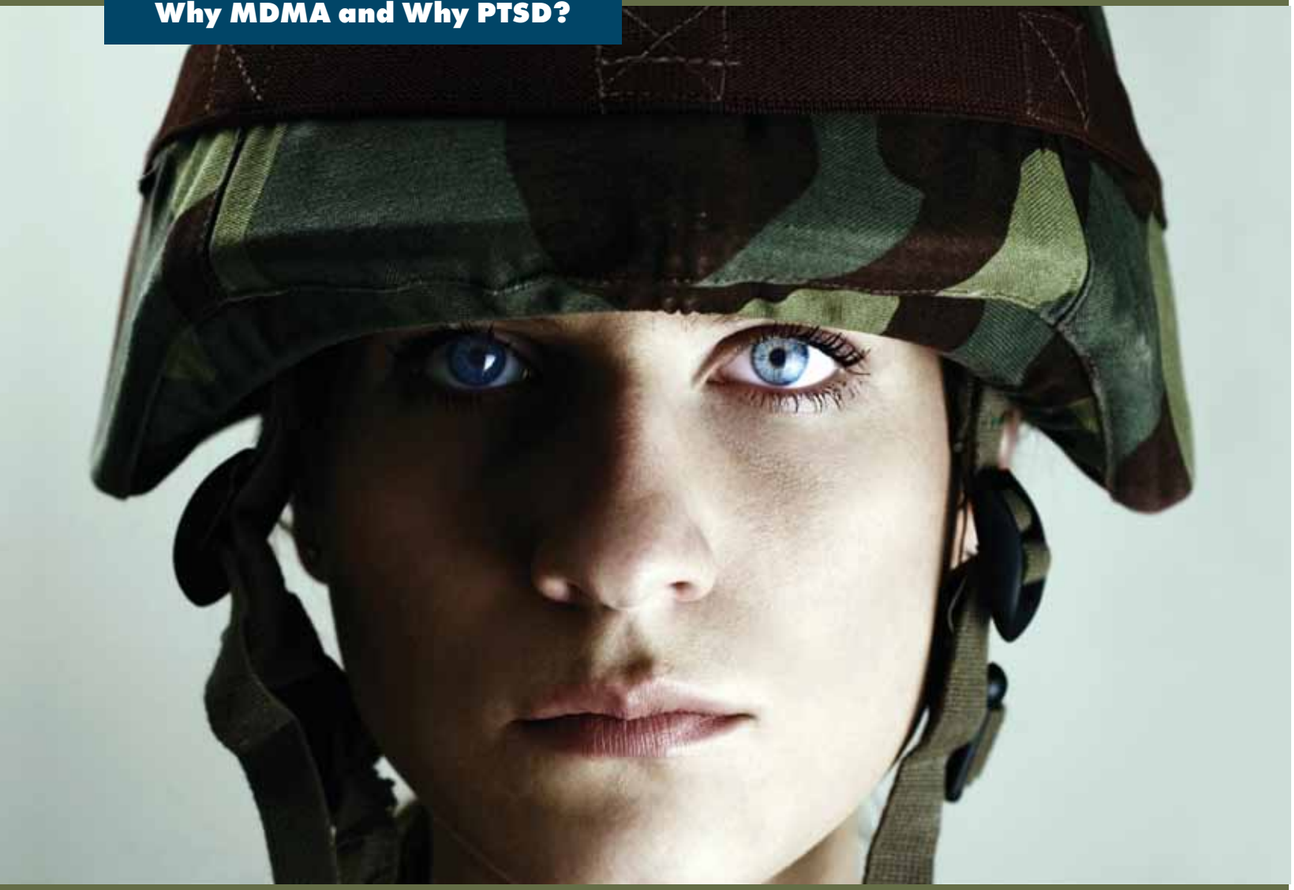
a monopoly on their sale.

For-profit pharmaceutical companies

have shown no interest

in developing these drugs.

Why MDMA and Why PTSD?



As increasing numbers of U.S. soldiers return home with posttraumatic stress disorder (PTSD) after serving in Iraq and Afghanistan, it's our national priority and ethical obligation to develop more effective treatments for PTSD. MAPS is responding by conducting a series of Phase 2 pilot studies in order to demonstrate to the public and regulatory agencies that MDMA-assisted psychotherapy can be used as a remarkably effective medical treatment for chronic, treatment-resistant PTSD patients who are inadequately helped by currently available treatments. On July 19, 2010, the results of our first Phase 2 pilot study were published in the Journal of Psychopharmacology. Out of 20 subjects in the study, over 80% in the experimental group no longer met the diagnostic criteria for PTSD, compared with 25% in the placebo group.

In 2009, the U.S. Veterans Administration spent about $5.5 billion on PTSD disability payments to approximately 275,000 veterans, with costs and numbers of veterans with PTSD continuing to increase. During an appearance at a gathering of mental health professionals on October 26, 2009, **U.S. Secretary of Defense Robert Gates stated, *"Beyond waging the wars we are in, treatment of our wounded, their continuing care, and eventual reintegration into everyday life is my highest priority...I consider this a solemn pact between those who have suffered and the nation that owes them its eternal gratitude."***

"It's basically like years of therapy in two or three hours. You can't understand it until you've experienced it."

–former Army Ranger who participated in a MAPS-sponsored pilot study, quoted in Military.com, March 2009

The primary reason for selecting MDMA as our initial drug target is that it offers patients a unique, gentle, yet profound experience of self-acceptance and an enhanced ability to feel and integrate complex, challenging emotions. Compared to other psychedelics like LSD or psilocybin, MDMA has minimal effects on perception or one's sense of self-control. This makes MDMA a suitable drug to administer to psychedelic-naïve patients as well as to therapists in training to administer MDMA-assisted psychotherapy.

Another major reason for working initially with MDMA is that over the last 25 years, the nations of the world have spent over $300 million on basic research into the risks of MDMA/Ecstasy, with all of that research in the public domain. A search on Medline for the terms MDMA or Ecstasy results in over 4,000 published papers. As a result of the enormity of the existing body of research, the funding necessary for our drug development program is drastically reduced, since we do not have to repeat these basic safety studies. Concerns about toxicity have decreased over the past decade due to this body of research. Toxicity concerns are further minimized in our therapeutic model because MDMA is administered only a few times within a three to four month period of therapy, and only under the direct supervision of a therapist team (we require male/female co-therapist teams). This is in contrast to existing medications, which are administered daily for months, years, or often indefinitely.

PTSD is our top priority clinical indication in large part because MDMA possesses unique pharmacological and psychological properties that may make it especially well suited for use as an adjunct to psychotherapy with PTSD patients. In addition, PTSD is a worldwide public health problem and is typically a chronic illness associated with high rates of psychiatric and medical co-morbidity, disability, suffering, and suicide. An array of psychotherapeutic options exist for treating PTSD and two SSRIs (sertraline and paroxetine) are approved as PTSD treatments by the FDA. However, a significant minority of PTSD patients fail to respond adequately to established PTSD psychotherapies, or respond in ways that are statistically significant but clinically inadequate. The existing evidence demonstrates that the combination of pharmacotherapy and psychotherapy is more effective in treating PTSD than either pharmacotherapy or psychotherapy alone. Once approved, MDMA will be the first medication that works by enhancing the psychotherapeutic process, unlike other pharmacotherapy treatments that are administered on a daily basis primarily to reduce symptoms.

Q: What is MDMA?

A: MDMA is a unique medication that has the potential to enhance the psychotherapeutic process by helping people confront painful thoughts and memories with reduced fear, and helping them form a therapeutic alliance with the psychotherapists. MDMA is currently classified as a Schedule I substance, meaning that it can be legally administered to humans only in the context of a research study. MAPS' goal is to sponsor rigorous research that proves safety and efficacy to the satisfaction of the FDA so that MDMA-assisted psychotherapy can be legally prescribed.

Michael Mithoefer, M.D., and Annie Mithoefer, B.S.N.

(Photo: The Washington Post Magazine)

"Because of MDMA's reported ability to decrease levels of fear and defensiveness and increase the sense of trust, we hope that will be a catalyst for the therapeutic process."

–Michael Mithoefer, M.D., MAPS-sponsored therapist, quoted in The Washington Post, March 2004

Peter Oehen, a psychiatrist in the Swiss town of Biberist, says substances such as MDMA can produce results where conventional psychotherapies fail. "They help overcome the wall of denial that some patients build up," said Oehen.

–quoted in USA Today, April 2008

"Patients in our study had a fear of the fear. Something about the MDMA made it possible for them to approach the feared thought, the feared 'place' in their mind – and when they got there, it wasn't as terrible as they thought. A lot of these people, the light bulb went off, they had the insight, but there's still a lot of work to do. They've had this for years, it's shaped their lives, and now they have to rebuild them."

–Mark Wagner, Ph.D., MDMA/PTSD study independent rater, quoted in The Washington Post, November 2007

Patients say...

Donna Kilgore in The Washington Post Magazine

(Photo: The Washington Post Magazine)

Before becoming the first patient treated by Michael and Annie Mithoefer in the flagship MDMA-assisted psychotherapy study sponsored by MAPS, Donna Kilgore had suffered from posttraumatic stress disorder for over ten years. Donna had been the victim of a brutal rape in her home in 1994. For years she experienced symptoms of PTSD, including nightmares and an even more frightening sense of numbness towards her life and family. "It was what it must feel like to have no soul," she says. It wasn't until her symptoms escalated to flashbacks, panic attacks, fainting spells, and migraine headaches that she sought treatment and was quickly diagnosed with PTSD. She followed a regimen of various antidepressants and tried dozens of different therapists and forms of therapies, but nothing worked. "I was getting to the point where it was either go sit on a mountaintop or go dive off a cliff." That was until she tried MDMA-assisted therapy.

"Before, I knew
the path was through
the battlefield,
but I just could not
get through it.
[But during MDMA therapy]
I knew I could
walk through it,
and I wasn't afraid."
–Donna

Spotlight on MAPS Clinical Team Members Amy & Berra

Amy and Berra traveled to Solothurn, Switzerland on February 28, 2010 for a site visit, to our MDMA/PTSD and LSD/end-of-life anxiety studies, where they assisted researchers to ensure that all regulatory requirements were being met and study protocols and procedures were followed.

Amy Emerson brings over fifteen years of experience in the pharmaceutical industry to her work guiding MAPS' ever-expanding clinical research program. While she may have left the for-profit world behind, her experiences managing Phase 1, 2, and 3 clinical trials have provided MAPS with the regulatory know-how to work with the FDA to move psychedelic research forward.

Prior to joining MAPS, Amy worked her way up at Novartis from Clinical Research Associate to Clinical Program Manager. Then in 2001, Amy attended the Mind States conference in Berkeley, California. At the time she was intrigued by the idea of applying her extensive knowledge of clinical trials to the untapped field of psychedelic research, but it wasn't until 2003 when she learned of MAPS' plan to conduct clinical trials of MDMA-assisted psychotherapy for PTSD that she found an organization working towards that goal. Amy's expertise in clinical research complemented the MAPS vision to put scientifically grounded research to work towards gaining FDA approval for the therapeutic use of psychedelics.

Over the past seven years, Amy has helped to facilitate the growth of MAPS' clinical research program from vision to a professionally run group that consistently implements the many complex and interlocking tasks necessary for conducting multiple clinical trials under the jurisdiction of multiple regulatory agencies.

Berra Yazar-Klosinski, Ph.D., draws on her scientific training and experience in clinical research in order to support MAPS' pioneering efforts in research to develop psychedelics as prescription pharmaceuticals.

Berra joined MAPS in search of a clinical research position with an organization where profit didn't dictate scientific research. After earning her Bachelor's of Science in Biology from Stanford University, Berra spent a year working as a Research Associate for Millennium Pharmaceuticals on Phase 1 clinical trials of pharmaceutical treatments for Acute Myeloid Leukemia. While experience in the for-profit pharmaceutical industry honed her research skills, MAPS' philosophy appealed to her because "a drug isn't just going to be dropped because it is not being pursued for profit."

Berra holds a Ph.D. in Molecular, Cell, and Developmental Biology from the University of California, Santa Cruz, an achievement which will allow her to continue coordinating MAPS' clinical trials, as well as to lead her own research investigating the neurobiological mechanisms underlying MDMA-assisted therapy. Berra currently has a funding proposal under review with the National Institute for Mental Health, which would support research into the role that MDMA plays in facilitating the release of oxytocin and other neurotransmitters using samples from the upcoming study of MDMA-assisted therapy with veterans with war-related PTSD. This research could provide a model for the neurobiological mechanisms underlying MDMA-assisted psychotherapy in treating PTSD.

MAPS Clinical Development Plan: MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder (PTSD)

Executive Summary

After investing over $1.5 million and 25 years of dedicated effort, MAPS has completed two successful "Proof of Principle" pilot studies of MDMA-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder (PTSD). Both MAPS' U.S. study (N=21) and Swiss study (N=12) were conducted without producing any Serious Adverse Events (SAE) or evidence of harmful effects. Our U.S. study produced statistically and clinically significant evidence of substantial efficacy. On July 19, 2010, a paper about the study was published in the *Journal of Psychopharmacology*. Our Swiss study had fewer subjects and produced clinically significant evidence of efficacy that approached statistical significance (0.1), with average reductions in PTSD symptoms larger than that obtained in the studies of Zoloft or Paxil that resulted in their approval by the FDA for the treatment of PTSD. MAPS' successful U.S. and Swiss studies are the foundation of the Phase 2 portion of our strategic MDMA prescription drug development plan and are essential milestones in the advancement of MDMA toward approval as a prescription medication.

In order to develop a drug into a prescription medicine, several phases of clinical trials must be conducted. In general, Phase 1 trials test the safety of a drug in healthy populations of between 10 and 100 subjects, Phase 2 trials gather preliminary information on the safety and efficacy of the drug to treat the condition under investigation in populations of 12 to 200 subjects, and Phase 3 trials gather conclusive evidence regarding efficacy and safety in larger populations of 250 to 2000 subjects. At least two Phase 3 studies are required to prove safety and efficacy before permission for prescription use can be approved. If the drug proves to be safe and efficacious in two Phase 3 studies, the sponsor of the studies submits a New Drug Application (NDA) to the FDA and/or the European Medicines Agency (EMEA), which review the application for possible approval as a prescription medicine.

The U.S. and Swiss results make a compelling case for advancing an MDMA/PTSD drug development effort aimed toward an FDA End-of-Phase 2 meeting, with a parallel meeting with the EMEA. The goal of these meetings are for MAPS, the FDA, and EMEA to come to an agreement on the design of the two large-scale, multi-site Phase 3 studies that will serve as the basis for approval. MAPS now has the opportunity to build on the promise of the successfully completed U.S. and Swiss pilot studies by conducting further research in preparation for these End-of-Phase 2 meetings. MAPS currently has four additional MDMA/PTSD studies in the protocol development and approval stage, involving sites in the U.S., Canada, Israel, and Jordan. Completing these studies and preparing for the End-of-Phase 2 meeting will require approximately $1.7 million in funding over three years (see chart on following page).

After completing our proposed series of MDMA/PTSD Phase 2 pilot studies, the next key decision point for MAPS will take place after the End-of-Phase 2 meeting, when the design of the Phase 3 studies has been determined and the cost of the Phase 3 studies can be estimated. Our best current estimate is that the two Phase 3 studies combined will involve about 560 subjects, cost about $8 million, and take three to five years to conduct and evaluate. Ideally, one Phase 3 study would take place in about 15-20 sites in the U.S. and Canada and one in about 15-20 sites in Europe and the Middle East. After the protocol design and cost estimates are refined following the End-of-Phase 2 meetings, a decision will be made whether to move forward with these Phase 3 studies. If we do move forward, and if the data from these studies is supportive, MAPS will submit a New Drug Application (NDA) to the FDA and EMEA for MDMA-assisted psychotherapy for PTSD. From that point it will take approximately one to two years for final review and approval by the FDA and EMEA.

Should approval be granted, the addition of MDMA-assisted psychotherapy as a treatment option for PTSD could make a major contribution to improved mental health for PTSD patients around the world and would facilitate the development of MDMA and other psychedelics for a wide range of other psychotherapeutic uses.

In order to build on our successful Proof of Principle studies, MAPS is seeking donations totaling $1.7 million over the next two years to make possible an international series of Phase 2 MDMA/PTSD pilot studies which will lead to the next phase of research with the U.S. FDA. We've developed relationships with non-profits in other countries so that donors from outside the U.S. should contact us to see if they could obtain tax-deductions in their own countries. We invite you to join with us and donate, to whatever extent you are able, so that MAPS can continue to work towards developing MDMA and other psychedelics into culturally-accepted, legal prescription medicines.

MAPS International Research Strategy

MAPS has chosen, for several reasons, to conduct some of our MDMA/PTSD pilot studies outside of the U.S. In the first few years after obtaining permission in the U.S. for our initial pilot study, we were concerned about the possibility of a politically motivated backlash (due to the history and stigma surrounding research with psychedelics) causing permission to conduct this study to be withdrawn. We decided to seek approval for research from regulators in other countries so the FDA would see its risk/benefit analysis independently affirmed elsewhere, and would be more comfortable with its decision to let us proceed. Now that we have generated promising data in our U.S. and Swiss studies, and have obtained a "may proceed" letter from the FDA for our next U.S. MDMA/PTSD study that will enroll only veterans, we feel a backlash at the FDA is unlikely. We have also been impressed with and grateful for the supportive nature of the staff with whom we've worked at the FDA. It has become clear from our meetings with the FDA that they will require us to conduct research in accordance

Multidisciplinary Association for Psychedelic Studies (MAPS)

Phase 2 MDMA/PTSD Studies Expenses

In Preparation for 2013 FDA/EMEA End-of-Phase 2 Meeting as of July 26, 2011

STUDY	Actual 2008-09	Actual 2009-10	Actual 2010-11	2011-12	2012-13
U.S. MDMA/PTSD Flagship Study	$194,600	$110,000	$19,241	$3,000	$0
U.S. MDMA/PTSD Flagship Long-Term	$0	$3,939	$7,507	$2,000	$0
U.S. MDMA/PTSD Flagship Relapse Study	$0	$0	$5,845	$16,500	$8,500
U.S. MDMA/PTSD Veterans Study	$1,570	$35,806	$147,600	$235,000	$111,355
U.S. MDMA/PTSD Veterans Long-Term	$0	$0	$0	$0	$10,000
Swiss MDMA/PTSD Study	$48,000	$33,500	$30,666	$3,000	$0
Swiss MDMA/PTSD Long-Term	$0	$0	$5,000	$0	$0
Israel MDMA/PTSD	$13,250	$27,308	$33,696	$125,000	$81,948
Israel MDMA/PTSD Long-Term	$0	$0	$0	$0	$10,000
Canadian MDMA/PTSD	$21,600	$9,814	$8,615	$90,000	$150,584
Canadian MDMA/PTSD Long-Term	$0	$0	$0	$0	$10,000
Jordanian MDMA/PTSD	$3,470	$31,456	$21,458	$50,000	$29,666
Jordanian MDMA/PTSD Long-Term	$0	$0	$0	$0	$5,000
Australian MDMA/PTSD Study	$0	$0	$0	$25,000	$25,000
Australian MDMA/PTSD Long Term	$0	$0	$0	$5,000	$0
US MDMA/PTSD Intern Study	$0	$0	$0	$50,000	$200,000
US MDMA/PTSD Intern Study Long Term	$0	$0	$0	$0	$10,000
ASSOCIATED PROJECTS	**2008-09**	**2009-10**	**2010-11**	**2011-12**	**2012-13**
End-of-Phase-2 Meeting with FDA/EMEA	$0	$0	$0	$0	$50,000
MDMA Literature Review	$3,340	$3,256	$6,063	$3,500	$3,500
MDMA Treatment Manual/NIMH grant	$640	$8,752	$5,219	$7,500	$5,000
MDMA Therapist Training-Protocol	$9,600	$15,038	$17,652	$10,000	$25,000
MDMA Researcher Retreats	$7,236	$27,067	$2,092	$0	$25,000
Mithoefer Supervisory/PR TIme	$0	$27,951	$33,975	$62,500	$64,500
MDMA Research General	$1,830	$11,404	$54,911	$55,000	$15,000
Clinical Research General	$13,360	$38,036	$38,885	$45,000	$35,000
Total MDMA-Related Expenses	**$318,496**	**$383,327**	**$438,425**	**$783,000**	**$875,053**
Multi-Year Projected Costs	**$1,658,053 over next two years**				

In order to build on our successful "Proof of Principle" studies, MAPS is seeking donations of $1.7 million over the next two years to make possible an international series of Phase 2 MDMA/PTSD pilot studies to make possible the next phase of research with the U.S. FDA.

with the rigorous standards of state-of-the-art scientific methodology that apply to all pharmaceutical drug development research, and will not obstruct our studies because of irrational fears or drug war-related political considerations.

The other reason for our international studies is to see if we could lay the groundwork for one of the two required Phase 3 multi-site studies to take place in the U.S. and Canada and the other in Europe and the Middle East. Both the FDA and the European Medicines Agency (EMEA) generally require one of the two large-scale, multi-site Phase 3 studies to be conducted domestically, while the other could be conducted abroad. By cross-submitting our U.S./Canadian Phase 3 study data to the EMEA and our European and Middle East Phase 3 study data to the FDA, we may be able to obtain prescription approval in the U.S. and Europe simultaneously. This could save many millions of dollars and several years in obtaining approval from the EMEA. If we conducted both of our Phase 3 studies in the U.S., we would still need to conduct another Phase 3 study in Europe. However, there are substantial challenges in conducting research abroad with cultural differences that may influence the therapeutic outcomes and language differences that complicate our training and monitoring tasks. As we prepare for our End-of-Phase 2 meetings, we'll first review the outcomes of our studies conducted in Europe and the Middle East and compare them to our outcomes from studies inside the U.S. and Canada. Then we'll decide whether to continue with our international strategy or focus on conducting our two Phase 3 studies entirely in the U.S. and Canada.

MDMA/PTSD Study in Veterans, U.S.

Our current top-priority study is our ongoing Phase 2 pilot study of MDMA-assisted psychotherapy for 16 U.S. veterans with chronic, treatment-resistant, combat-related PTSD. This study uses our most sophisticated design and was the first protocol that the FDA accepted as designed, without requesting a single change. This study has full approval from all regulatory agencies and review boards and is now enrolling and treating subjects.

This new study builds on our flagship Phase 2 clinical trial of MDMA-assisted psychotherapy (published July 2010 in the *Journal of Psychopharmacology*) in several ways. First, by separating the subjects into three groups (each group receiving different doses of MDMA) rather than two (each group receiving either a full dose of MDMA or an inactive placebo), we hope to get more detailed information about the role of MDMA in determining treatment effectiveness. Second, we hope to show that we can maintain an effective blind in these studies and affirm the scientific validity of clinical trials of psychedelic psychotherapy. Finally, since our previous study primarily involved female survivors of sexual abuse and assault, we hope this study will show that the benefits of MDMA-assisted psychotherapy extend to the population of veterans with war-related PTSD.

The study is being conducted by co-therapists Michael Mithoefer, M.D., and Annie Mithoefer, B.S.N., in Charleston, South Carolina. We currently have a waiting list of veterans who want to volunteer, and we are still seeking additional subjects. The design of this study is testing what may become the design of one of our Phase 3 studies. This study is a three-arm study, with eight subjects receiving three experimental sessions of our standard full dose of 125 mg, followed about two hours later by 62.5 mg; four subjects receiving a medium dose of 75 mg, followed about two hours later with 37.5 mg; and four subjects receiving a threshold/low dose of 30 mg, followed about two hours later by 15 mg. This design is likely to be the most effective in producing inaccurate guesses as to which dose was received, perhaps resulting in an effective double-blind.

By cross-submitting our U.S./Canadian Phase 3 study data to the EMEA and our European and Middle East Phase 3 study data to the FDA, we may be able to obtain prescription approval in the U.S. and Europe simultaneously. This could save many millions of dollars and several years...

The EMEA has issued guidelines for the design of research for drugs to treat PTSD. The EMEA wants to see studies in different patient groups who differ in the cause of PTSD, specifically war-related PTSD as compared to PTSD resulting from sexual assault or childhood sexual abuse. It's our preliminary view that the cause of the PTSD doesn't matter in terms of the design of our treatment program with MDMA-assisted psychotherapy. The two veterans in our initial U.S. pilot study responded as well as the women with PTSD from sexual assault or childhood sexual abuse. Should the results of this study in veterans with war-related PTSD prove similar to those we obtained

in our flagship U.S. study, we would then be able to design our Phase 3 studies to enroll people with PTSD regardless of whether the cause of their PTSD was war-related or related to sexual assault or abuse. Should we learn that veterans require a differently designed treatment program than people whose PTSD is related to sexual assault or abuse, we would need to design our Phase 3 studies to treat one group or the other.

The cost of this study is projected to be $595,000. In this three-arm design, we have more subjects than usual who could enroll in Stage 2 (open label MDMA administration) since fully half the subjects (8) will receive less than the full-dose in the randomized portion of the study. As a result, the cost is about $31,000 per subject (16) since we're likely to repeat the entire 4-month treatment process 24 times, rather than just 16. The cost also includes over $90,000 in travel expenses that we pay for the subjects, an expense that will be substantially reduced in our Phase 3 studies once we have 15-20 different treatment locations in the U.S.

This study is going to be the subject of a documentary directed by Jordan Kronick, who worked with Peter Jennings on "Ecstasy Rising," the most thorough and balanced major-media documentary made to date on MDMA.

U.S. MDMA/PTSD Flagship Pilot Study (complete)

MAPS worked for 18 years, starting in 1986, to obtain the necessary approvals for our first pilot study conducted under an FDA Investigational New Drug (IND) application to investigate the therapeutic use of MDMA-assisted psychotherapy, which was approved in 2004. The experimental treatments in this randomized, double-blind, placebo-controlled study in 21 subjects were completed in late 2008. On July 19, 2010, the outstanding results were published in the peer-reviewed *Journal of Psychopharmacology*, and became the journal's most downloaded paper in 2010. We have recently completed a long-term follow-up of subjects in this study (see below).

Michael Mithoefer, M.D., board-certified in psychiatry and emergency medicine, and his female co-therapist Annie Mithoefer, B.S.N, psychiatric and cardiac nurse, conducted this study as a husband/wife co-therapist team. This study, including data analysis and writing a scientific paper, cost $1.25 million, much of which was due to the FDA and numerous Institutional Review Boards (IRBs) prolonging the specific protocol approval process for four years while imposing exceptionally cautious and expensive procedures. With 21 subjects, this study cost about $57,000 per subject, a cost that we've substantially reduced in our other studies.

The results at our two-month follow-up were remarkable, with over 80% of the subjects who went through the MDMA-assisted psychotherapy no longer having sufficient symptoms to be diagnosed with PTSD, as compared to 25% of the placebo group. The effect size was larger than for Zoloft or Paxil or any of the existing evidence-based psychotherapies.

During the course of the study, we successfully negotiated several protocol amendments with the FDA and our IRB. We increased from two to three the number of MDMA-assisted psychotherapy sessions, which were scheduled about three to five weeks apart with weekly non-drug psychotherapy for integration and preparation. We obtained permission to administer a supplemental dose of MDMA, half the initial dose given about two hours afterwards, in order to prolong the plateau of optimal therapeutic effects. We also obtained permission to offer all subjects who received the placebo the option to enroll in the study a second time (Stage 2) with open-label, full-dose MDMA, starting after the two-month follow-up after their final experimental session in the randomized study. This Stage 2 design is useful scientifically, since the placebo subjects become their own controls in a cross-over study. It also helps with recruitment and retention of placebo subjects throughout the entire four-month treatment program. All of our pilot studies are now designed to use supplemental dosing and include the option for placebo subjects to enroll in an open-label Stage 2 with full dose MDMA after their two-month follow-up following their final experimental session.

The results at our two month follow-up were remarkable, with over 80% of the subjects who went through the MDMA-assisted psychotherapy no longer having sufficient symptoms to be diagnosed with PTSD, as compared to 25% of the placebo group. The effect size was larger than for Zoloft or Paxil or any of the existing evidence-based psychotherapies.

The subjects in our first U.S. study were mostly women survivors of sexual assault or childhood sexual abuse, along with two male veterans of the Iraq War. The subjects' average duration of PTSD was over 19 years. The results at our two-month follow-up were remarkable, with over 80% of the subjects who went through the MDMA-assisted psychotherapy no longer having sufficient symptoms to be diagnosed with PTSD, as compared to 25% of the placebo group. The effect size was larger than for Zoloft or Paxil or any of the existing evidence-based psychotherapies. However, this was just a small pilot study. In addition, our treatment program is more expensive and requires more therapist time than any of the other treatments. The main limitation of this study was that we used an inactive placebo, since we needed to have a baseline of side effects that could not be attributed to MDMA. We asked the therapists and subjects to guess whether the MDMA or the placebo had been administered. The therapists always guessed correctly, and subjects almost always guessed correctly. Now that we have obtained our baseline of side effects, all other studies use active placebo, most often consisting of a low, sub-threshold dose of MDMA.

U.S. MDMA/PTSD Intern Study

The next phase (Phase 3) of our clinical development plan for MDMA-assisted psychotherapy for PTSD will require many more male/female co-therapist teams than are currently available. Finding a cost-effective and sustainable way to recruit effective therapists is therefore a top priority. MAPS is currently planning a Phase 2 "intern study" in which we will investigate the effectiveness of MDMA-assisted psychotherapy for PTSD when one member of the standard male/female co-therapist team is a healthcare intern (being trained in therapy, social work, or nursing). The other member of the team will be a professional therapist trained in our treatment method. As interns work for free in exchange for fulfilling required training hours under professional supervision, this approach would reduce costs and train the next generation of psychedelic therapists. This study will take place in Boulder, CO, and will be led by Clinical Investigator Marcela Otalora, M.A., L.P.C. Subjects will be U.S. veterans with chronic, treatment-resistant PTSD, mostly from the Iraq, Afghanistan, or Vietnam wars, along with survivors of childhood sexual abuse, assault, rape, and others. This study is still in the protocol development stage, and is expected to cost $250,000.

U.S. MDMA/PTSD Long-Term Follow-Up Study

MAPS recently completed a long-term follow-up study of subjects who participated in our flagship Phase 2 pilot study of MDMA-assisted psychotherapy for PTSD. This study was intended to determine whether the outstandingly positive results of the original study persisted over time. The preliminary analysis shows that benefits from treatment with MDMA-assisted psychotherapy were maintained over time. An average of 41 months (about 3 and a half years) after completing the study, average scores on the Clinician-Administered PTSD Scale (CAPS) were statistically equivalent to those measured at the end of the treatment period. A few subjects did experience relapses, and these individuals will be eligible to enroll in our "relapse

study" (see below). MAPS' clinical research team is currently preparing a manuscript detailing the results of the study. The paper is co-authored by Michael Mithoefer, M.D., Mark Wagner, Ph.D., Annie Mithoefer, B.S.N., Ilsa Jerome, Ph.D., Scott Martin, M.D., Berra Yazar-Klosinski, Ph.D., Tim Brewerton, M.D., and Rick Doblin, Ph.D. Once the manuscript is complete, it will be submitted for publication in a peer-reviewed scientific journal.

of MDMA-assisted psychotherapy for PTSD. The study already has clearance both from the Food and Drug Administration (FDA) and an independent Institutional Review Board. Now that we have received all necessary clearances, we can begin enrolling subjects. The new study will take place in Charleston, SC, and will be conducted by co-therapists Michael Mithoefer, M.D., and Annie Mithoefer, B.S.N., and is limited to up to three subjects whose

Diagnostic Scale (PDS), which is the secondary measure of PTSD symptoms completed by the subjects, also showed statistically significant improvements in symptoms after treatment.

The therapeutic results obtained in our previously completed U.S. flagship study of MDMA-assisted psychotherapy for PTSD were larger than those from our Swiss study. In order to determine how

These cultural differences will require us to think ever more carefully about the core elements of our therapeutic approach and how we teach them to our therapist teams. In addition, perhaps one day, our Israeli and Jordanian teams could meet together to discuss their shared research using MDMA-assisted psychotherapy to heal trauma.

U.S. MDMA/PTSD Relapse Study
Our long-term follow-up to our flagship Phase 2 clinical trial of MDMA-assisted psychotherapy for PTSD revealed that although over 80% of the subjects in our previous study no longer met criteria for PTSD two months after treatment, for several subjects symptoms did eventually return. Benefits from MDMA-assisted psychotherapy tended to persist over time during the long-term follow-up, conducted an average of 41 months after treatment. Our new "relapse study" will attempt to determine whether a single additional open-label MDMA-assisted psychotherapy session along with several non-drug psychotherapy sessions can enable these subjects to once again be free of a PTSD diagnosis.

The Drug Enforcement Administration (DEA) has approved the Schedule I licenses required to transport, store, and administer the MDMA for our new "relapse study"

PTSD symptoms returned after participating in our flagship study of MDMA-assisted psychotherapy for PTSD.

MDMA/PTSD Study Switzerland
Conducting research in multiple international sites allows us to improve our research methodology by comparing results. In January 2011, the final long-term follow-up visit was completed in MAPS' Swiss study of MDMA-assisted psychotherapy for PTSD. On June 1, the clinical research team closed and locked the database, officially concluding the data collection portion of the study. A preliminary analysis suggests that the Clinician-Administered PTSD Scale (CAPS), which is the primary measure of PTSD symptom severity, showed a trend towards improvement after treatment, with CAPS reductions somewhat larger than in comparable studies of Zoloft and Paxil. The Posttraumatic

methodological, personnel, and/or cultural differences may have led to these differences, we are asking a series of questions about whether there were differences in (1) the population from which subjects were drawn, (2) the recruitment process, (3) the screening process, (4) the demographics of the subjects enrolled, (5) Swiss and American cultural approaches to PTSD, (6) the approaches of the various independent raters, and (7) the way in which subjects' PTSD symptoms were treated and/or evaluated by the clinicians. The answers to these questions will help MAPS understand how best to maximize therapeutic outcomes.

The clinical team is now assisting Clinical Investigator Peter Oehen, M.D., and co-author Ulrich Schneider, M.D. (former president of the International Society for Traumatic Stress Studies) in preparing a manuscript to be published in a peer-reviewed

scientific journal. The quality inspection of the final data set from our Swiss study revealed remarkably clean results, with a 0.04% error rate (far below the 0.5% required to pass). The locked database will also be used for our final report to the U.S. FDA.

MDMA/PTSD Study Canada
The goal of our 12-person Canadian study, designed similarly to our Swiss study, is to learn if we can replicate the outstanding results of our U.S. study. Our Canadian study will be conducted in a similar cultural context as our U.S. study. Ingrid Pacey, M.D., a psychiatrist and certified Grof Holotropic Breathwork practitioner, and Andrew Feldmar, M.A., a Hungarian-Canadian psychologist and disciple of R.D. Laing, are the male/female co-therapists conducting this study. Both of these experienced and highly trained therapists worked with MDMA-assisted psychotherapy prior to its criminalization and share a theoretical orientation with our U.S. and Swiss teams. We're using two senior therapists in Canada to give us the best chance to replicate the outstanding U.S. results. Once approved, this study will be the first psychedelic research study in Canada since the mid-1970s.

The cost of this study is projected to be $310,000, about $26,000 per subject. This cost is due in large part to our treatment team consisting of two senior therapists each in private practice, as compared to our teams in both the U.S. and Swiss studies, which consisted of a psychiatrist and a much lower paid nurse. Fortunately, the cost is lower than it would otherwise be because the therapists are both working at a discounted rate. To reduce costs substantially in future studies, we're planning to explore pairing one trained therapist with an opposite-sex student in training to become a co-therapist, while keeping a close eye on the efficacy data to learn whether therapist cost reductions can be generated without substantially reducing efficacy (see U.S. intern study). Depending on the results at the half-way point, we might modify the Canadian protocol design after the study has completed treating half the subjects (6) by splitting Dr. Pacey and Andrew Feldmar into two teams, with each of them paired with an opposite-sex student in training to become a co-therapist.

Each of these new teams would treat three additional subjects. With this possible design modification, even though the numbers are low and there could be meaningful differences in patients that obscure the differences in therapist teams, we would still be able to compare average efficacy when two senior therapists were working together to when each was working with a student/trainee.

Canadian regulations require that the study pharmacy be adequately secure, and that the proper accountability procedures are in place. In order to ensure compliance, Health Canada must inspect the study pharmacy and agree that it meets all requirements. The final step before initiating the study will be to obtain the license to import the MDMA for the study into Canada from Switzerland (where another MAPS MDMA/PTSD study was recently completed).

Health Canada inspected the Vancouver pharmacy that will be used to store and label the MDMA capsules. On July 6, 2011, we received a letter from Health Canada requesting additional information about the site and about how we proposed to transfer the MDMA from the pharmacy to the treatment facility. A follow-up inspection was conducted on October 18, though security requirements have now changed and additional security measures may be needed.

MDMA/PTSD Study Israel
Building on our experience with previous studies, MAPS has determined that pairing traditionally trained psychiatrists with others with more direct experience working with altered states of consciousness may help produce a more effective therapeutic team. For this reason, our new Israeli study of MDMA-assisted psychotherapy for PTSD will employ three (rather than two) male/female co-therapist teams in order to increase enrollment rates and provide more opportunities for therapists to learn from each other. The variety of expertise brought to the therapeutic sessions by these co-therapist teams should make them more effective at achieving positive treatment outcomes.

The study has the full approval of Israeli regulatory bodies including the Israeli Ministry of Health and

an Ethics Committee. The protocol will also be submitted to the U.S. FDA, which must prospectively approve the study before we can start enrolling subjects since it is being conducted under a U.S. Investigational New Drug (IND) application.

In January 2011, MAPS researchers Michael Mithoefer, M.D., and Annie Mithoefer, B.S.N., conducted a training course for therapists who will be conducting the treatment sessions in the new study. The training took place over five days, with the first three days in Tel Aviv in the basement of a house built by MAPS Founder Rick Doblin's great-grandfather in 1923. The therapists reviewed MAPS' treatment manual for MDMA-assisted psychotherapy for PTSD, videos of actual treatment sessions from our completed U.S. MDMA/PTSD study, and were familiarized with the study protocol.

The study will be conducted at Be'er Ya'akov Mental Health Center outside Tel Aviv, in a dedicated area in a standalone building separate from the main facility which includes a separate bathroom and kitchen. The grounds include orange groves and walking paths, making it a secure and comfortable site for conducting the sessions.

MDMA/PTSD Study Jordan
MAPS is working to conduct an MDMA/PTSD pilot study in Jordan as part of our efforts to explore whether MDMA-assisted psychotherapy can be successfully conducted in a range of cultural contexts. These cultural differences will require us to think ever more carefully about the core elements of our therapeutic approach and how we teach them to our therapist teams. In addition, perhaps one day, our Israeli and Jordanian teams could meet together to discuss their shared research using MDMA-assisted psychotherapy to heal trauma.

The study is currently awaiting clearance from the Jordanian Food and Drug Administration (JFDA). The Principal Investigator will be Nasser Shuriquie, M.D., the former chief military psychiatrist for the Jordanian Royal Medical Services. Dr. Shuriquie is now Clinical Director and Deputy General Manager at Al-Rashid Hospital in Amman, Jordan, the largest mental health and addiction treatment

hospital in Jordan and a teaching hospital for the entire region.

This is a 12-person study. The first two subjects will be enrolled in an open-label full dose lead-in, to help us train the Jordanian co-therapists and to enable them to gain experience using our treatment method. MAPS staff will use the adherence measures to quantify therapist adherence to our treatment method as described in our treatment manual. We'll use our standard treatment model of three experimental sessions, scheduled about three to five weeks apart, with weekly non-drug psychotherapy for purposes of preparation and integration.

The remaining ten subjects will be enrolled in the randomized, double-blind, placebo-controlled portion of the study. We'll use the same full dose that we are using in our other studies, 125 mg followed about two hours later with 62.5 mg. We'll use 40 mg, followed by 20 mg about two hours later, as our low-dose/placebo. This low dose of 40 mg is unique to this study and will help us gather additional information about the effectiveness in producing a double-blind with a range of doses.

The study has approval from the Ethics Committee at Al-Rashid Hospital, and has met all requirements for liability insurance. On July 30, 2011, we learned that the JFDA decided not to approve the protocol for our Jordanian study of MDMA-assisted psychotherapy for PTSD at this time, based in part on comments from an expert reviewer chosen by the JFDA. We anticipate receiving a further set of questions from JFDA, and we are hopeful this study will eventually be approved.

U.S. MDMA/PTSD Study Australia
Planning for Phase 3 of our MDMA-assisted psychotherapy for PTSD research program involves determining which study sites and which cultural contexts are most likely to produce the most significant results. Conducting our ongoing series of Phase 2 clinical trials in a variety of international contexts helps us determine whether and to what extent the effectiveness of MDMA-assisted psychotherapy for PTSD depends on language and culture, as well as subject demographics and independent rater variables.

MAPS is now working with a group of researchers in Australia to plan a new study of MDMA-assisted psychotherapy for subjects with chronic, treatment-resistant PTSD. This study is in the protocol development process. We are hoping to have it submitted to an Institutional Review Board by the beginning of 2012 and then to the Therapeutic Goods Administration (the Australian equivalent of the U.S. FDA). The lead investigators and co-therapists will be Stuart Saker, M.D., a psychiatrist with the Australian armed forces, and clinical psychologist Fiona MacKenzie, M.Psych, another married male/female co-therapist team. Michael Mithoefer, M.D., the lead investigator for our U.S. MDMA/PTSD studies, will be the official medical monitor.

The formal sponsor for the study will be the newly formed Australian research organization Psychedelic Research in Science and Medicine (PRISM). PRISM, created by Martin Williams, Steve McDonald, Jonathan Carmichael, and others, is officially incorporated as a legal organization and has submitted its application for tax-deductible status. The study will be conducted in a non-institutional setting rather than in collaboration with an academic or military organization, just as in our U.S., Swiss, and Canadian studies. The total cost for this study is estimated at $250,000, of which MAPS has pledged $50,000.

U.S. MDMA/PTSD Therapist Training Protocol
This protocol is in healthy subjects, rather than in subjects with PTSD. This protocol is a placebo-controlled, double-blind, randomized, cross-over study that allows MAPS to administer a single MDMA-assisted psychotherapy session to up to 20 therapists as part of their training to conduct MAPS' MDMA/PTSD studies, while also conducting a series of evaluations of the psychological effects of MDMA administered to healthy volunteers in a therapeutic context. This study is now enrolling and treating subjects. Clinical Investigators Michael Mithoefer, M.D., and Annie Mithoefer, B.S.N., are leading the study, and Julie Holland, M.D., is the medical monitor.

We initially requested permission to administer one session of MDMA-assisted psychotherapy to therapists as part of our training program. We made the case in our initial protocol submission that therapists would likely be more effective administering MDMA to their patients if they had a subjective understanding of the effects of pure MDMA from a direct, personal experience. Since MDMA is a controlled substance, the only way we could provide a legal training experience would be in the context of a clinical study. The FDA replied that there was no model for them to approve a training protocol. Instead, they recommended that we design a Phase 1, randomized, double-blind, placebo-controlled cross-over study that would gather useful data in a methodologically rigorous manner. If we could accomplish that, the FDA would permit us to limit enrollment to therapists from the U.S. and around the world who had first completed our non-drug training program. We subsequently designed a study of the psychological effects of MDMA on healthy volunteers that met the requirements of the FDA and we were given permission to proceed with the subjects in our training program. We then submitted the protocol to our IRB, which after extensive discussions also permitted us to proceed. We were profoundly encouraged by this demonstration of the FDA's willingness to listen to us and to propose ways that their concerns could be fully addressed.

We will have trained raters to evaluate videotapes of the psychotherapy sessions using the new criteria that we've developed to quantify therapist adherence to the principles in our treatment manual. We'll use this evaluation as a teaching tool to help us in more effectively training our therapist teams in order to standardize our therapeutic approach across therapist teams with different languages, cultures, and nationalities.

"As a member of the clinical research community, I was asked to review MAPS' conduct of clinical trials and provide guidance. I was incredibly impressed by the clear mission to bring the high standard of clinical research and International Conference on Harmonization (ICH) guidelines to all of MAPS' research, and to ensure that data generated would be held with the same level of integrity and respect as larger, established research institutes."

— Felicia Lipansky, Senior Project Manager, Onyx Pharmaceuticals, MAPS volunteer

Profile of MAPS Founder and Executive Director Rick Doblin, Ph.D.

In 1972, at age 18, while attending New College of Florida, Rick decided to devote himself to becoming a psychedelic psychotherapist and researcher, at the same time that psychedelic research around the world was being shut down due to political reasons. Rick was influenced by the Holocaust and the Vietnam War to work on addressing the psychological causes of war and scapegoating, recognizing that human technological evolution has far exceeded human emotional and spiritual evolution. In 1982, Rick heard about MDMA when it was still legal. In 1984, anticipating that the DEA would soon move to criminalize MDMA, Rick co-founded a non-profit organization to organize MDMA therapists and coordinated a DEA Administrative Law Judge lawsuit to block criminalization of the therapeutic use of MDMA. The non-profit won the lawsuit but the DEA still found a way to criminalize all uses of MDMA. Rick founded MAPS in 1986 to move MDMA, psychedelics and marijuana through the FDA drug development research and approval process. In 1991, as part of Rick's training to become a psychedelic psychotherapist, Rick was among the first people to be certified by LSD researcher Dr. Stanislav Grof as a Holotropic Breathwork practitioner. Holotropic Breathwork is a technique of deep breathing that can produce experiences similar to those produced by psychedelics. In 2001, Rick earned a Ph.D. in Public Policy from the Kennedy School of Government at Harvard University. Rick's dissertation focused on the regulation of the medical use of psychedelics and marijuana. He has been working diligently, and successfully, putting this plan into effect ever since. Rick is married to Lynne Jones Doblin and they have three children, all teenagers: Eden (17), Lilah (15), and Eliora (13).

"MDMA opens the doorway for people

to feel deep feelings of love and empathy,

which is the core of being human.

We should be looking at that

and learning from that."

—MAPS Executive Director Rick Doblin, Ph.D.

Quoted in The Washington Post, March 2, 2004

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"It meant the world to me to be able to look at the fear, to look at the shame. I didn't know I was ashamed. It was like I'd been wearing the scarlet letter. It was so heavy. When I got out of that session, I felt a hundred pounds lighter... [MDMA] gave me the ability not to fear."

—Donna, a patient in a MAPS-sponsored pilot study, reflecting on her MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD) brought on by childhood sexual abuse

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