Research News

Treating PTSD with MDMA-Assisted Psychotherapy

Phase 3 Trials Starting Fall 2018

MAPS and the MAPS Public Benefit Corporation (MPBC) are making excellent progress towards the initiation of our upcoming Phase 3 trials of MDMA-assisted psychotherapy for PTSD. Our open-label lead-in study is progressing smoothly, with most of the 15 sites ready for the Phase 3 trials. We expect that by the time you read this, we will have started recruitment and enrollment for our main Phase 3 double-blind, multi-site, randomized controlled trial.

As of July 31, 2018, MPBC clinical research staff have completed 13 out of 14 Study Initiation Visits for our open-label lead-in study of MDMA-assisted psychotherapy for PTSD at planned Phase 3 sites across the United States and Canada. The purpose of this study is to provide the final training for our Phase 3 co-therapy teams, to ensure the scalability of the trials to a multi-site study, and to collect additional safety data about the administration of MDMA-assisted psychotherapy. Each new co-therapy team will work with a single participant at their respective study site with supervision provided by MAPS' therapy training team. The open-label lead-in study includes about 85 therapists and 40 co-therapist teams. Also as of July 31, 20 participants have been enrolled and treated in the open-label lead-in study—approximately half of the planned sample size—and five have completed the study. Eighteen of 20 treated have seen clinical significant decreases in PTSD symptoms.

On July 10, the DEA Schedule 1 license was approved for the Boston, Mass., Phase 3 study site. On July 24, Health Canada approved the Section 56 exemption (for controlled substances) for our Montreal study site. The University of Wisconsin-Madison study site is still awaiting its DEA Schedule 1 license. We are still in discussions with the Israeli Ministry of Health about approvals for our two planned Israeli Phase 3 sites. The remainder of the open-label sites have received all approvals and are ready for Phase 3.

MAPS' Phase 3 trials, starting in the summer of 2018, will assess the efficacy and safety of MDMA-assisted psychotherapy in adult participants with PTSD at sites in the U.S., Canada, and Israel. Over a 12-week treatment period, participants will be randomized to receive 12 90-minute non-drug preparatory and integration sessions, along with three day-long sessions of either MDMA or placebo in conjunction with psychotherapy, about a month apart. The primary endpoint will be the Clinician Administered PTSD Scale (CAPS-5), as assessed by a blinded pool of independent raters.

MAPS' Phase 3 trials will be conducted at the following sites:

- Los Angeles, CA | private practice
- San Francisco, CA | research institution
- San Francisco, CA | private practice
- Boulder, CO | private practice
- Fort Collins, CO | private practice
- Farmington, CT | research institution
- New Orleans, LA | private practice
- New York, NY | research institution
- New York, NY | private practice
- Charleston, SC | private practice
- Madison, WI | research institution
- Boston, MA | research institution
- Montreal, Canada | private practice
- Vancouver, Canada | research institution
- Israel | research institution (2)

These Phase 3 trials build on the promising results of MAPS' completed Phase 2 trials. Phase 3 studies are the final phase of research required by the FDA before deciding whether to approve MDMA as a legal prescription treatment for PTSD, which MAPS projects will happen by 2021. Once approved, MDMA will be required to be used in conjunction with psychotherapy in a clinical setting.

In MAPS' completed Phase 2 trials with 107 participants, 56% no longer qualified for PTSD after treatment with MDMA-assisted psychotherapy, measured two months following treatment. At the 12-month follow-up, 68% no longer had PTSD. Most subjects received just 2–3 sessions of MDMA-assisted psychotherapy. All participants had chronic, treatment-resistant PTSD, and had suffered from PTSD for an average of 17.8 years. Based on these results, the FDA granted Breakthrough Therapy Designation to MDMA-assisted psychotherapy for PTSD in August 2016.

MAPS and MPBC are excited to reach this milestone toward bringing the healing potential of MDMA-assisted psychotherapy to those suffering from PTSD. As of July 31, we have reached our funding goal of $26.7 million for the US Phase 3 studies required to gain approval from the FDA for MDMA-assisted psychotherapy for PTSD. Additional funds will be needed for post-approval commercialization expenses, for Expanded Access, for the production of commercial current Good Manufacturing Practices (cGMP)-certified MDMA, our ongoing MDMA Therapist Training Program, and for approval in the European Union through the European Medicines Agency (EMA), as well as for post-approval Phase 4 studies. After the FDA approves legal prescription sales of MDMA, MPBC will be able to cover some of its further research costs through income from the sales of MDMA and the training of therapists, supplementing funding from donations.

There is now a clear path ahead to make MDMA a legal medicine for millions of people suffering from PTSD. Help heal trauma: **maps.org/donate.**

Discussions Started for European EMA Phase 3 Trials—and New Trials in South America

On June 12, 2018, MAPS and MPBC staff met in London with the Scientific Advice Working Party (SAWP) of the European Medicines Agency (EMA). On June 28, the SAWP sent us their written scientific advice regarding our Phase 3 protocol and overall drug development plans. Our team had the benefit of consulting with Xavier Luria, the former Head of Safety and Efficacy of Medicines at the EMA, who also led our team in several practice meetings prior to the SAWP meeting. Overall, the SAWP is sympathetic to our efforts and are willing to let us proceed toward a Phase 3 protocol design, though with a larger size than we originally proposed.

Our original proposal was to include approximately 20 PTSD subjects in an initial European open-label therapist training protocol, where MAPS' therapist trainers monitor videotapes and provide supervision, with another 50 subjects in the controlled Phase 3 study. The EMA requested an increase in the proposed sample size, so we're now proposing to include 70 subjects in the controlled Phase 3, with 35 subjects receiving our manualized therapy with inactive placebo and 35 receiving our manualized therapy with active MDMA. The SAWP also suggested adding additional countries for geographic diversity throughout the European Union. In addition to sites in the UK (2), Netherlands (2), Germany (2), and Czech Republic, we plan to include Phase 3 sites in Finland and Portugal. There may be additional EU sites trained to support investigator-sponsored MDMA research.

In their June 28 scientific advice letter, SAWP was happy with our proposals for MDMA manufacturing as well as toxicology and pharmacology research, and they will allow us to draw from existing scientific literature for approval for the studies. We will likely apply for PRIME (Priority Medicine Scheme, similar to Breakthrough Therapy Designation in the US but with a much lower acceptance rate), a new EMA program to "enhance support for the development of medicines that target an unmet medical need."

From September 27–October 3, 2018, in Landgraaf, The Netherlands, MPBC staff and researchers will conduct a training for approximately 60 therapists who will be participating in European Phase 3 MDMA-assisted psychotherapy for PTSD trials or related research in Europe and elsewhere. Participants will come from many countries, including Australia, Afghanistan, the UK, Netherlands, Germany, the Czech Republic, Spain, Slovakia, Norway, and Finland. This training will be Part B of MAPS' MDMA Therapy Training Program (**maps.org/training**), in which participants will view video case studies of Phase 2 clinical trial sessions and dialogue about therapist competencies. After the training, those who go on to work on a MAPS-sponsored research protocol will go on to complete the remainder of the training program, including experiential trainings (Part C), role-plays (Part D), and supervised therapy sessions (Part E), with optional participation in our therapist training protocol in which subjects receive MDMA in a therapeutic setting. The next European training will take place in January 2019. In the remainder of 2019, we're planning at least five subsequent trainings in the US to train therapists for Expanded Access and post-approval prescription use.

MAPS and MPBC staff in discussions with the European Medicines Agency (EMA) in London, June 2018. L to R: Michael Mithoefer, M.D.; Berra Yazar-Klosinski, Ph.D., Rick Doblin, Ph.D.; and Amy Emerson.

Overall, we are pleased to report that (1) MAPS' efforts to work with the EMA are moving forward well; (2) we're likely to be able to move to Phase 3 research; (3) we'll need to increase the number of subjects and countries for Phase 3 research in the EU, but if Phase 3 generates proof of safety and efficacy, more countries will be ready to review applications for marketing authorization; (4) EMA research is more complex than FDA research; and (5) we have not yet started negotiations with the national health care systems which will ultimately pay for most of the patients who will be treated in the EU.

Excitingly, we're also making progress with MDMA research in South America. In June 2018, the first MDMA-assisted psychotherapy session took place in our open-label therapist training study in Brazil. We've also learned that if we can conduct an eight-person open-label therapist training study in Colombia, and if we have either FDA or EMA approval, Colombia would also approve prescription use of MDMA-assisted psychotherapy for PTSD. MAPS founder and executive director Rick Doblin, Ph.D., believes that many small countries around the world will approve the prescription use of MDMA-assisted psychotherapy for PTSD once we obtain either FDA or EMA approval, and conduct very small open-label therapist training studies in those countries.

Approval from the EMA will require additional funds. MAPS currently estimates that European Phase 3 trials will cost

about $9 million—about one third of the US Phase 3 costs. This efficiency is due to the fact that all the data we provide to the FDA can also be submitted to the EMA.

MDMA Production and Encapsulation

On March 13, 2018, the MDMA that will be used in the Phase 3 clinical trials, and in our toxicology and clinical pharmacology studies, was successfully imported into the United States from our third-party pharmaceutical vendor in the UK. The compound, manufactured by Onyx Scientific Ltd. using a synthetic precursor, is certified under current Good Manufacturing Processes (cGMP), and was synthesized using the same route that will be used to manufacture MDMA for post-approval sales.

As of August 1, we were in the second round of testing for the clinical trial randomization system, working with a third-party vendor providing an FDA-compliant randomization system.

On August 30, 2018, the MDMA that will be used in MAPS' upcoming Phase 3 clinical trials of MDMA-assisted psychotherapy for PTSD is planned to be shipped by our third-party cGMP drug product manufacturer, Sharp Clinical Services, Inc. (US), to the approved study sites. Sharp has received all the necessary distributor licenses, will be performing the encapsulation, and is now manufacturing the MDMA capsules. They will be provided in blister packs specially marked for the clinical trials after Sharp has completed the manufacture of the placebo capsules and the demonstration batch, examined the blend and content uniformity between capsules, determined the dissolution protocol (how quickly the capsules dissolve), and generated stability data.

Drug product formulation studies are complete for the immediate release solid oral dosage form. Hydroxypropylmethyl cellulose (HPMC) capsules will be prepared by third-party cGMP drug product manufacturer, Sharp Clinical Services, Inc. (US). The final formulation includes only MDMA, mannitol, and magnesium stearate. Based on preliminary studies conducted with our previous MDMA supply for Phase 1 and Phase 2 trials, the drug product achieved greater than 80% dissolution at 15 minutes, indicating that the active compound is immediately and completely released from the capsules within 15 minutes. Based on only small differences in formulation, the Phase 3 and commercial formulations are anticipated to be comparable.

As the MDMA dosing regimen is three single-dose treatments per patient, the planned amount of drug product needed for commercial distribution is far lower than approved medications requiring daily dosing.

Plans for Expanded Access in the US

In the coming year, once Phase 3 trials of MDMA-assisted psychotherapy for PTSD are underway, MAPS plans to apply for a special FDA program called Expanded Access, which allows the use of an investigational medical product (one that has not yet been approved by the FDA) outside of a clinical trial. The program's purpose is to grant access to potentially beneficial investigational treatments for people facing a serious or immediately life-threatening condition for which there is no satisfactory treatment currently available. The FDA's website has more information on the Expanded Access program (**fda.gov**). If Expanded Access for MDMA-assisted psychotherapy for PTSD is approved, new sites may obtain approval to administer MDMA-assisted psychotherapy to eligible patients with treatment-resistant PTSD, under a MAPS protocol. MAPS has had promising preliminary discussions with both the FDA and DEA about the Expanded Access program.

An online application for potential Expanded Access sites and their therapy providers will be posted on the MAPS website once MAPS has applied for Expanded Access, anticipated early 2019. An announcement about the application will also be made through the MDMA Therapy Training Newsletter (**maps.org/training**). Since Expanded Access is a U.S. FDA program, only sites in the U.S. and U.S. territories may participate. International programs may become available in the future. The first opportunity for potential Expanded Access providers to receive trainings is expected in March 2019.

Update on the MDMA Therapy Training Program

From June 24–30, 2018, MAPS-sponsored researchers Dr. Michael Mithoefer and Annie Mithoefer, BSN, led a training in Marshall, Calif., in MDMA-assisted psychotherapy for PTSD for approximately 90 students, the largest group MDMA therapy training ever conducted. The trainees consisted of students in the California Institute of Integral Studies (CIIS)' Certificate in Psychedelic-Assisted Therapies and Research (CPTR) program, plus about 30 guests, including a large proportion of medical doctors and psychotherapists, including visiting clinicians and researchers from Israel, the Czech Republic, and Puerto Rico.

From July 16–19, 2018, MAPS-sponsored researchers Dr. Michael Mithoefer and Annie Mithoefer, BSN, Marcela Ot'alora, and Bruce Poulter, together with MAPS Executive Director Rick Doblin, Ph.D., MPBC Executive Director Amy Emerson and MPBC Associate Director of Training and Supervision Shannon Carlin participated in a four-day meeting in Boulder, Colo., to further develop the training program for MAPS-sponsored MDMA researchers and potential Expanded Access sites. Work included adapting the program for a larger audience, planning refinements to the *Treatment Manual* (**maps.org/treatmentmanual**), conducting a revision of the online training module (Part A), and building a standard format for in-person therapy trainings. The purpose of these adaptations is to prepare for the upcoming FDA Expanded Access program in 2019, which will involve a massive expansion of the number of people participating in these trainings.

As of August 1, 2018, 66 participants have been treated in our therapist training protocol for MAPS-sponsored MDMA therapy researchers, growing our capacity to include more trained researchers in the expanding field of MDMA therapy research. For more information about the MDMA Therapy Training Program, visit **maps.org/training**.

Policy and Advocacy News

Update on MAPS' Efforts to End the NIDA Monopoly on Marijuana for Research

by SGT(R) Jonathan Lubecky, MAPS Veterans & Governmental Affairs Liason

Federal cannabis policy has been stalled for the past six months by U.S. Attorney General Jeff Sessions. MAPS continues to engage in a concerted effort to end the National Institute on Drug Abuse (NIDA) monopoly on marijuana for federally regulated research in the U.S., which Sessions continues to protect. In these efforts, MAPS has engaged in multiple strategies involving the Executive and Legislative branches of government, as well as multiple non-governmental organizations. We have met with staff in the offices of Senators Grassley (R-IA), Harris (D-CA), Hatch (R-UT), Tillis (R-NC) and Schatz (D-HI), as well as numerous staff from other offices who have expressed a specific desire to evolve on the issue and are now, at least in part, turning to MAPS for unbiased fact-based information concerning not just cannabis research, but also MDMA-assisted psychotherapy.

In April 2018, MAPS founder and executive director Rick Doblin, Ph.D., and I attended the House Veterans Affairs Cannabis Round Table, and have since formed relationships with a variety of veterans' organizations, including Iraq and Afghanistan Veterans of America, Veterans of Foreign Wars, American Legion, Paralyzed Veterans of America, and Disabled American Veterans. We have also engaged and strengthened relationships with more conservative and libertarian groups such as Americans for Tax Reform. I also attended Robert Wilkie's confirmation hearing in June where I had a brief discussion with him concerning ending the NIDA monopoly.

Pressure is building on Sessions from all corners for a multitude of reasons; the sense in Washington, D.C., is that everyone wants it to end, but few policymakers will expend much time on it. However, MAPS has worked to educate a few key influential senators, six of whom sent a letter on July 25, 2018, to Sessions to increase the pressure. The letter to Sessions states he has until August 10, 2018 to resolve the issue by granting additional licenses to grow marijuana for research. The letter was signed by Senators Grassley (R-IA), Schatz (D-HI), Gardner (R-CO), Gillibrand (D-NY), Klobucher (D-MN), and Coons (D-DE). During the debate on the CBD provisions of the recently passed Farm Bill, Sen. Grassley introduced an amendment which, among other things, would have ended the NIDA monopoly. One of the best tools we have in this debate is the Attorney General's own words about how we "must obey the law even if we don't like it" and then calmly point out, as the Senators did in their letter, that the Attorney General is in fact in violation of federal law by failing to meet legal deadlines for reviewing and responding to all applications for licenses to end the monopoly. In addition, MAPS is planning to prepare and file a lawsuit against the Drug Enforcement Administration (DEA) and Sessions if no actions are taken by the August 10, 2018, deadline proposed by Senators Hatch, Grassley, Harris, and others.

Jonathan Lubecky and Rick Doblin at the House Veterans Affairs Committee Roundtable, April 2018. (Photo: George Allen)

In order to increase pressure on Sessions, we have launched a campaign to convince various allied conservative-leaning and veterans groups to sign on to a letter demanding an end to the NIDA monopoly. We are also reaching out to State Representatives and Senators, some of whom, such as Eric Brakey (R-ME), are also running for Senate or House seats. The goal is to have local elected officials apply pressure to their own states' Congressional delegations.