FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING (PDAC)

Tuesday, June 4, 2024

8:30 a.m. to 5:43 p.m.

Meeting Roster

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Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

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Satish Iyengar, PhD

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(Chairperson)

Attending Psychiatrist

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UPMC Western Psychiatric Hospital

Professor in Radiology and Psychiatry

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. NARENDRAN: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking, and also a reminder to everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. For media and press, please contact the FDA Office of Media Affairs. Their email is currently displayed.

My name is Dr. Narendran, and I will be chairing this meeting. I will now call the June 4, 2024 Psychopharmacologic Drugs Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We'll start with the agency to my left and go around the table.

DR. STEIN: Good morning. Dr. Peter Stein, Office of New Drugs, FDA.

DR. BURACCHIO: Teresa Buracchio, Director

of Office of Neuroscience, FDA.

DR. FARCHIONE: Tiffany Farchione, Director of the Division of Psychiatry, FDA.

DR. KIM: Jean Kim, Clinical Team Leader, Division of Psychiatry, FDA.

DR. YANG: Peiling Yang, Supervisory Mathematical Statistician, Division of Biometrics I, FDA.

DR. LaCIVITA: Cynthia LaCivita, Director of Division of Risk Management, FDA.

DR. BARONE: Melissa Barone, Clinical Psychologist at the VA Maryland Health Care System.

DR. HOLTZHEIMER: Paul Holtzheimer, Deputy Director for Research at the VA's National Center for PTSD and Professor of Psychiatry and Surgery at Geisel School of Medicine at Dartmouth.

DR. DUNN: Walter Dunn, Psychiatrist and Assistant Clinical Professor at the University of California Los Angeles, Semel Institute for Neuroscience and Human Behavior, and Section Chief for Mood Disorders at the Greater Los Angeles VA Healthcare System.

DR. NARENDRAN: Raj Narendran, Psychiatrist, UPMC, University of Pittsburgh.

DR. FRIMPONG: Joyce Frimpong, Designated Federal Officer, FDA.

DR. FIEDOROWICZ: Jess Fiedorowicz, University of Ottawa and the Ottawa Hospital.

DR. IYENGAR: Satish Iyengar. I'm from the Department of Statistics at the University of Pittsburgh.

MS. WITCZAK: Kim Witczak, consumer rep with Woodymatters, Minneapolis.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant, patient representative. I am a sociologist and a qualitative research consultant at the Injury Prevention Research Center at UNC Chapel Hill.

DR. HERTIG: John Hertig, Pharmacist, Associate Professor, and Immediate Past Chair of the Department of Pharmacy Practice, Butler University College of Pharmacy and Health Sciences.

DR. AMIRSHAHI: Maryann Amirshahi. I'm a Professor of Emergency Medicine at Georgetown University. I'm an emergency medicine physician,

medical toxicologist, clinical pharmacologist, and addiction medicine physician, as well as the Medical Director of D.C. Poison Control.

DR. REBO: Elizabeth Rebo. I'm the Executive Director of Pharmacy Quality and Medication Safety for Kaiser Permanente, National Pharmacy Services.

DR. CANUSO: Carla Canuso from Janssen Research and Development, a Johnson & Johnson company. I'm the non-voting industry representative.

DR. NARENDRAN: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Frimpong will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. FRIMPONG: Thank you.

The Food and Drug Administration is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting

members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect

the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of new drug application 215455 for midomafetamine, MDMA, capsules submitted by Lykos Therapeutics for the proposed indication of treatment of posttraumatic stress disorder. The committee will be asked to discuss the overall benefit-risk profile of MDMA, including the potential public health impact. This is a particular matters meeting, which specific matters related to Lykos

Therapeutics' NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Carlo Canuso is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Canuso's role at this meeting is to represent industry in general and not any particular company. Dr. Canuso is employed by Johnson & Johnson, Janssen.

We would like to remind members and temporary voting members that if discussions involve any other products or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. NARENDRAN: We will now proceed with the FDA's introductory remarks starting with Dr. Tiffany Farchione.

FDA Opening Remarks - Tiffany Farchione

DR. FARCHIONE: Good morning, everyone, and welcome to this meeting of the Psychopharmacologic Drugs Advisory Committee. Today we're going to discuss Lykos Therapeutics' application for midomafetamine for the treatment of posttraumatic stress disorder or PTSD. This application is both consequential and complex. To set the stage, I want to provide a brief overview of some of the issues we'll be discussing today.

PTSD is a severe and disabling psychiatric condition. It's characterized by intrusive

memories; hyperarousal; and avoidant behavior following exposure to traumatic events. Comorbidities are common, and PTSD is associated with a high risk for suicidal ideation and behavior. Patients with PTSD experience impairments in social and occupational functioning and diminished quality of life.

There are currently just two medications approved to treat PTSD, the selective serotonin reuptake inhibitors, paroxetine and sertraline, and these approvals were roughly 25 years ago. Response rates for individuals with PTSD treated with SSRIs rarely exceed 60 percent, and a fraction of patients achieve full remission. Thus, there remains a significant unmet need for additional safe and effective treatments.

As you are no doubt aware, there's been a surge in interest in the therapeutic potential of psychedelic drugs in the last several years, with much of that interest focused on psychiatric indications, including PTSD. As an agency, we've used the term "psychedelics" as shorthand to

include classic psychedelics like psilocybin and LSD, as well as midomafetamine.

Midomafetamine is also known as 3,4-methylenedioxymethamphetamine, or MDMA, a Schedule I controlled substance. Although midomafetamine does not typically produce the types of perceptual disturbances characteristic of classic psychedelics, it does produce prolonged alterations in mood, empathy, and judgment. The nature of the experience may differ, but the impact on trial design and interpretability is very similar.

The application we'll be discussing today presents a first-in-class treatment for PTSD and a novel treatment paradigm. The applicant's proposed treatment regimen consists of three sessions of midomafetamine administration, in conjunction with psychological intervention, for a single 4-month course of treatment. The midomafetamine program is the first psychedelic drug development program to reach the new drug application stage.

This is also the first commercial drug

development program for any psychedelic. The initial IND for midomafetamine was submitted in 2001, and that perspective is important. In the last 20 years, and especially in the last 5 or 10 years, we've gained a lot of experience reviewing psychedelic applications and understanding their unique challenges. Last year, we even issued a guidance for considerations for clinical trials with psychedelics in which we outlined foundational constructs that all sponsors studying therapeutic potential of psychedelic drugs should consider. But we've been learning as we go along. So even though we have a guidance now, that doesn't mean that all of the advice in that guidance will be reflected in the studies that you'll hear about today.

In this application, we have two positive studies. Participants appear to experience clinically meaningful durable improvement in their PTSD symptoms; however, several factors make these data challenging to interpret and complicate the overall benefit-risk assessment for this

application.

Chief among these factors is the nature of the treatment itself. One of the biggest challenges in designing adequate and well-controlled trials of psychedelics is that the acute effects of these drugs make it merely impossible to blind the studies. We call this functional unblinding. The trials may be designed and conducted as double-blind studies, but because of the effects of the drug itself, participants, and likely the investigators as well, are able to guess the treatment assignment. This in turn makes it difficult to know how much of the observed treatment effect is true benefit and how much is due to expectation bias.

It's important to note that it may still be possible for a study that is partially functionally unblinded to be considered an adequate and well-controlled study if there are adequate methods to minimize bias. Additionally, it's important to consider the magnitude of the treatment effects and the robustness of the study results, particularly

if the effects do not appear to be consistent with what is known about the natural history of the condition.

The applicant incorporated blinded central raters in an effort to minimize investigator bias in their phase 3 studies, but there were no study design elements intended to minimize expectation bias on the part of participants. We do have data from an unblinding questionnaire that we use to assess the extent of functional unblinding, and as expected, the vast majority of participants were able to accurately guess their treatment assignment. Unfortunately, the impact of that unblinding on the trial cannot be quantified.

It is reasonable to consider other data in an effort to understand whether the observed effects can be considered reliable. For instance, although it's unknown how long expectation bias might last, it may be reasonable to expect that an effect driven by expectation bias could wane relatively quickly. If this were true, it may also be reasonable to expect that a durable effect would

be more likely to be an effect attributable to the drug rather than to a placebo response.

So we advised the applicant to conduct follow-up assessments to explore the durability of response. That data was intended to be purely exploratory, but it's complicated for a number of reasons. First, about 25 percent of the participants dropped out between the parent study and the follow-up visit; and second, some participants used potentially therapeutic non-study drugs after the parent study and before the follow-up assessment. So these results are, again, difficult to interpret.

This is also an example of the learning as we go that I cited earlier. By the time that we advised the applicant to explore the durability of response with this open-label follow-up assessment, one of the two phase 3 double-blind studies was already completed and unblinded, not just functionally unblinded but actually unblinded. Participants in that study also had a longer time period between the parent study and the follow-up

visit. So these factors also impact interpretability, but they were a result of our late-stage advice.

So the applicant is proposing that midomafetamine serves to facilitate a psychotherapeutic intervention by enhancing emotional and cognitive processing of trauma. FDA does not regulate the practice of psychotherapy, but it is possible to include some language about therapy in a label, and even as part of an indication statement. If another mode of therapy is necessary in order to achieve a therapeutic response, we can say that the drug is indicated for use only in conjunction with the other mode of therapy.

But here, the contribution of psychotherapy to the overall treatment effect observed in these clinical studies has not been characterized. All of the treatment arms in all of the studies submitted included psychotherapy. The manualized therapy employed in this development program included therapeutic components that have been

previously studied in people with PTSD, but there have been no rigorous studies directly comparing this particular manualized therapy to other psychotherapeutic approaches or to midomafetamine alone without psychotherapy.

Nonetheless, with psychotherapy present in all treatment arms, the proposed paradigm of three midomafetamine medication sessions delivered over 4 months was superior to placebo for treatment of PTSD and remained superior to placebo at a long-term follow-up assessment. That said, the observed benefit in the placebo arm was also maintained at follow-up, suggesting that the therapy did provide some benefit. So if this product were to be approved, we can't label it for use on its own, but we also don't have strong evidence that the therapy is necessary to the observed effect.

In addition to the factors that complicate assessment of efficacy, the assessment of safety presents challenges. The adverse events reported in clinical trials are largely consistent with what

we know from the MDMA literature -- things like bruxism, muscle tightness, hyperhidrosis, and so on -- but the cardiac safety profile of midomafetamine is not well characterized and the QT assessment is incomplete. Study participants in the midomafetamine group experienced significant increases in both blood pressure and pulse that are, again, consistent with what we would expect from the MDMA literature.

Additionally, there are limited clinical laboratory data available for review. These issues would not necessarily impact the ability to approve the drug, but they would complicate our ability to write informative labeling and would likely necessitate additional postmarketing studies if we were to approve this product. However, it is the lack of data collection on the subjective effects of midomafetamine that may have the greatest impact on our regulatory decision making.

Although the agency had advised the applicant to collect adverse events that are associated with abuse, effects that were deemed

positive, favorable, or neutral -- things like euphoria or elated mood -- were not captured despite the fact that these effects are part of the evaluation of abuse potential as we outline in our guidance on this issue. There is extensive literature related to midomafetamine's abuse potential that can help inform our abuse potential assessment and scheduling recommendations, but the lack of data on the anticipated effects of midomafetamine makes it difficult to describe these effects in labeling or to characterize the duration of the effects to inform recommendations for patient monitoring.

That said, we do know that subjective effects of midomafetamine can persist for several hours, rendering patients in an impaired and vulnerable state that necessitates safety monitoring. Because of this prolonged impairment and vulnerability following midomafetamine administration, we required clinical trial protocols to include monitoring by two healthcare providers for the duration of the acute

midomafetamine experience; and if this product were to be approved, we believe that a risk evaluation and mitigation strategy, or REMS, will be necessary to ensure safe use and to mitigate the risks of serious harms that can result from patient impairment.

So to sum up, although this application presents a number of complex review issues, it does include two positive studies in which participants in the midomafetamine arm experienced statistically significant and clinically meaningful improvement in their PTSD symptoms, and that improvement appears to be durable for at least several months after the end of the acute treatment despite no additional doses of midomafetamine.

We're seeking the committee's input on whether the data contained in the submission are robust and persuasive enough to overcome the limitations of the studies that we have identified. We are also seeking the committee's input on the adequacy of the safety database and on risk mitigation strategies that may be needed if this

drug is approved.

Today we'll be asking the committee to respond to four discussion questions and two voting questions, which I'll quickly preview now so that you can keep them in mind during the presentations. First, we'll be asking you to discuss the evidence of effectiveness for midomafetamine for the treatment of PTSD, and we'll ask that you consider the potential impact of functional unblinding on the interpretability of the results, the durability of effect, and the role of the psychological intervention.

We'll also ask for you to discuss whether the available data are adequate to characterize the safety of midomafetamine. We'll ask that you consider the limited data collected on events deemed positive, favorable, or neutral; the lack of some clinical laboratory tests; and whether you have concerns about other safety issues and what additional data would be useful to characterize the safety of midomafetamine.

We'll ask that you discuss the potential for

patient impairment to occur with midomafetamine and the potential for serious harms that may result due to that impairment, and we'll ask you to discuss whether the proposed risk mitigation is sufficient to mitigate serious harms resulting from patient impairment. We'll ask that you include any additional safety monitoring conditions that you think are needed for safe administration and monitoring if this product were to be approved.

Finally, we'll ask you to vote, and the two voting questions, the first one is, do the available data show that the drug is effective in treating patients with posttraumatic stress disorder? And then we'll ask whether the benefits of midomafetamine with our proposed risk evaluation mitigation strategy outweigh its risks for the treatment of PTSD? Thank you.

DR. NARENDRAN: Thank you, Dr. Farchione.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee

meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including industry's non-employee presenters, to advise the committee of any financial relationships that they may have with the industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, including equity interests and those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Lykos Therapeutics' presentation.

Applicant Presentation - Amy Laverdiere

MS. LAVERDIERE: Good morning, Chair,

members of the committee, and members of the FDA. I'm Amy Laverdiere, Program Lead at Lykos Therapeutics. Thank you for the opportunity to present our data supporting midomafetamine assisted therapy, referred to as MDMA-AT, for the treatment of posttraumatic stress disorder, or PTSD, in adults.

PTSD is a serious mental health condition that immensely impacts patients' relationships, lifestyle, and quality of life, and can be life threatening. Combat veterans make up an important portion of the population with PTSD, but it can also develop in anyone who sees or experiences a traumatic event.

Regardless of causality, PTSD results in debilitating and lasting symptoms related to the trauma. These include reliving or re-experiencing the events through nightmares and flashbacks, and other changes in the person's thoughts, feelings, and emotions that may get in the way of their ability to sustain interpersonal relationships, hold gainful employment, and participate in daily

activities. PTSD is a strong predictor of disability, including functional, emotional, and medical impairments, and people with PTSD frequently experience anxiety, depression, substance-use disorder, and suicidal ideation.

While there have been advances in the management of PTSD, there have been no new FDA-approved treatments in over 20 years. Psychotherapy is the standard of care which has been shown to be reasonably efficacious; however, therapy alone can be challenging and often poses barriers to adequately address PTSD.

MDMA is not a new drug, and while it can be misunderstood due to its illicit counterpart, it actually has a well-documented history in the psychiatric field. In the 1970s and early 1980s, MDMA was used in conjunction with talk therapy by mental health providers since research suggested that MDMA allowed patients with psychiatric disorders to access, process, and communicate difficult emotions and experiences. It's been documented that about 4,000 people have been

administered MDMA in earlier clinical practice. In addition, about 2,000 participants have been included in more recent research studies. This historical experience, along with an extensive library of published literature, informed the design of our clinical program.

MDMA-AT has been studied across 17 clinical trials. Throughout clinical development, we've worked in close collaboration with the FDA. A special protocol assessment for our two nearly identical pivotal studies, MAPP1 and MAPP2, was agreed in 2017. Due to the seriousness of PTSD and the encouraging preliminary phase 2 data, MDMA-AT received breakthrough therapy drug designation that same year, and the NDA was submitted in 2023 and granted priority review.

MDMA is an entactogen that has the potential to be a powerful disease modifier. While the specific mechanisms are not completely understood, in the brain, MDMA is thought to be a monoamine reuptake inhibitor and releaser. We know psychotherapy can be effective, but only if

patients are able to tolerate the treatment. The available data and mechanism of action suggests that MDMA catalyzes the effectiveness of psychotherapy by facilitating memory recollection and extending the patient's window of tolerance for revisiting distressing thoughts or experiences.

Studies with MDMA show improved self-awareness and prosocial effects that enhance the therapeutic alliance between the patient and their therapist. By leveraging the effects of MDMA, individuals are more open to the potential benefits of psychotherapy. This psychological intervention includes aspects of established therapeutic approaches. This combination of MDMA plus psychological intervention provides patients with an acute treatment to reduce the symptoms associated with PTSD. The data generated from our clinical development program support our proposed indication for midomafetamine for the treatment of posttraumatic stress disorder, or PTSD, in combination with psychological intervention in adults.

Today, we'll share the data that support a positive benefit-risk profile for MDMA-assisted therapy. Across the two phase 3 studies, acute treatment with MDMA-AT resulted in statistically significant and clinically meaningful improvement in PTSD symptoms and improvements in functional impairment. We also have supportive evidence of durability through at least 6 months post-treatment.

The safety profile shows the drug was well tolerated with mostly transient mild-to-moderate, self-limiting adverse events expected for MDMA. There were low discontinuation rates throughout the program. Importantly, the favorable benefit-risk profile observed in the clinical trial setting will be supported by the proposed REMS; controlled distribution using single-dose packaging; labeling; therapist training; and provider and patient education.

With this information in mind, here is the agenda for the remainder of the presentation. We also have additional experts with us today to help

address your questions. All outside experts have been compensated for their time and travel to today's meeting. Thank you, and I'll now turn the presentation to Dr. Rosenbaum.

Applicant Presentation - Jerry Rosenbaum

DR. ROSENBAUM: Thank you, and good morning. I'm Jerry Rosenbaum, Psychiatrist and Chief Emeritus at Massachusetts General Hospital and Stanley Cobb Professor of Psychiatry at Harvard Medical School. I'm pleased to be with you today to provide a brief background on PTSD and the need for novel and effective interventions to address the highly prevalent suffering and functional impairment from this disorder.

My own principal efforts in this space include the co-founding of the Center for Anxiety and Traumatic Stress Disorders at MGH, serving recently as its director, and as a co-founder and oversight committee member of the MGH's home-based program for Veterans Suffer the Invisible Wounds of War, which now support thousands of veterans regionally and nationally.

PTSD is a serious, life-threatening, psychiatric disorder that emerges after traumatic experiences and currently effects more than 13 million adults in the United States, with patients experiencing their PTSD symptoms, on average, for more than six years. Of those treated, 40 to 60 percent of patients remain symptomatic with diagnosable PTSD.

Furthermore, 40 percent of patients go untreated entirely, mostly due to lack of available, accessible, or acceptable options, complicated by the daunting prospect of engaging in treatments that can prove ineffective while being challenging to undergo. And unfortunately, patients with PTSD have a 47 percent greater risk of mortality compared to patients without PTSD, often due to suicide but also other comorbidities.

Although PTSD is associated with exposure to deployment and combat, consequent to a number of potentially traumatic experiences, civilian trauma is actually more common. Individuals exposed to sexual violence, for example, or an unexpected

death in the family, or a life-threatening traumatic event may also develop PTSD. Understandably, a substantial subgroup of individuals who experience acute stress disorder after witnessing such traumatic events have enduring symptoms that go on to meet criteria for PTSD.

The American Psychiatric Association has established the DSM-5 diagnostic criteria. To meet criteria for a diagnosis of PTSD, symptoms must occur after an exposure to a traumatic event and continue for at least a month. These criteria are the basis for the CAPS-5, which is a tool used in clinical trials to assess the persistence and intensity of the symptoms.

To illustrate the four symptom clusters key to PTSD, here are some of the symptoms patients endure: distressing thoughts, intrusive memories or dreams, negative self-perception or self-blame, all of which can disturb sleep, social interactions, and work productivity.

The experience of PTSD does not begin and

end with diagnostic criterias, CAP scores, or even comorbidities. The haunting, intrusive, and pervasive traumatic memories with the associated anxious arousal and irritability reverberate through families, other loved ones, friends, and neighbors. Children and spouses especially are subject to the ravages or losses linked to withdrawal or angry eruption. Without effective treatment, the burden of PTSD can grow over time for the individual themselves and for also all those around them.

PTSD comes with a range of associated comorbid psychiatric conditions. This is often a complex patient population. For example, many individuals also have anxiety disorders, depression, substance-use disorders, and can experience suicidal ideation. In consequence, these comorbidities lead to increased healthcare utilization and worsened quality of life.

PTSD is a disorder about which there are still many unanswered questions regarding optimal psychological and pharmacological interventions.

Evidence-based psychotherapies are currently a mainstay of treatment and a first-line option recommended by treatment guidelines. The most widely recognized psychotherapies for PTSD include prolonged exposure, cognitive processing, and eye movement desensitization and reprocessing. These can be quite effective, though intolerable for some patients since they frequently exacerbate distress, as the patient may actually feel retraumatized in reliving their traumatic events.

While evidence-based therapies are mainly focused and time limited, other psychotherapies may be open-ended for months or years with uncertain results and high dropout rates. For patients that find psychotherapy challenging to tolerate, and particularly for those with comorbid depression and disabling anxiety or insomnia, pharmacologic treatments can be prescribed. Optimal treatment effect with antidepressant medications, for example, requires up to 12 weeks of daily dosing; however, response rates for individuals with PTSD treated with SSRIs, for example, rarely exceed

60 percent, and fewer than 20 to 30 percent of patients achieve a remission.

Ongoing pharmacological interventions may also be limited by tolerability issues and side effects. Several pharmacologic agents are used off label and concurrently despite lacking evidence of efficacy and not being approved for the PTSD indication, which speaks to the demand of prescribers for novel indicated therapeutics to provide our patients new tools to alleviate symptoms.

To conclude, PTSD is a serious and debilitating disorder. Patients experience chronic symptoms that disrupt their quality of life and impair function and health, and as I said, can be life threatening. Current treatments have limitations, some taking years with uncertain outcomes, and others are quite challenging for patients. Trauma-focused psychotherapy comes with substantial dropout rates and current pharmacologic options do not address the underlying cause of PTSD.

The field has acknowledged for years that we need to do better for our patients so they can experience symptom relief and successfully function in daily life. Effective interventions that address the core pathology of PTSD are desperately needed. We are compelled to seek innovative treatments with the potential to enhance our ability to treat this disorder. So I thank you, and I'll now turn the presentation over to Dr. Yazar-Klosinski to review the efficacy data.

Applicant Presentation - Berra Yazar-Klosinski

DR. YAZAR-KLOSINSKI: Thank you, Dr. Rosenbaum, and good morning. My name is Berra Yazar-Klosinski, Chief Scientific Officer at Lykos Therapeutics. It's been my honor to serve as the scientific lead for this development program for 15 years since the early phase 2 studies.

Today, I will share the data from two nearly identical phase 3 studies. MAPP1 included patients with at least severe PTSD and MAPP2 included patients with at least moderate PTSD. These studies support that MDMA in combination with

psychological intervention provides significant and meaningful reductions in PTSD symptoms and functional impairment in adults. Let me first begin with a brief overview of the study design.

MAPP1 and MAPP2 are randomized, double-blind, placebo-controlled clinical studies in patients with PTSD. These studies were conducted at 15 sites in the United States, Israel, and Canada. Potential patients were prescreened for eligibility and underwent three 90-minute preparatory psychotherapy visits indicated by yellow boxes in the first row.

Baseline efficacy assessments were conducted via live video conference between the second and third preparatory psychotherapy visits administered by a blinded independent rater, indicated by the purple triangle. Patients were randomized 1 to 1 to MDMA or placebo with identical psychological intervention.

Next, patients underwent their first medication session, which consisted of an 8-hour psychological intervention plus either MDMA or

placebo, indicated by the blue square. The treatment cycle also included three 90-minute integration psychotherapy visits. Between the second and third integration visits, patients met over live video conference with an independent rater who administered the efficacy assessments. This series of events was repeated for treatment cycles 2, and later 3. After the third treatment cycle, primary and secondary endpoints were assessed approximately 18 weeks following randomization. Note, this was about 2 months after the final medication session.

Let's turn to the dosing. The dosing regimen was determined based on early clinical use in the 1980s of MDMA with therapy. These findings were confirmed in the phase 2 program, which explored a range of doses with split dosing and dose escalation. In addition, there were independent studies of MDMA that studied the safety, pharmacology, and mechanism of action. These studies showed that MDMA is unique among PTSD treatments in that it does not require daily dosing

or steady state plasma levels to be effective. In fact, the medication is only taken in three medication sessions.

Following a single dose, onset of action occurs approximately 30 minutes post-administration with peak subjective effects around 70-90 minutes and effects persisting for 3 to 6 hours. Administering split doses 1 and a half to 2 hours apart was intended to facilitate an extension of the peak and more gradual subsidence of subjective effects. Subjective effects are those experienced internally by the patient.

The dose used in treatment session 1 was a split dose of 120 milligrams, and the dose was escalated to 180 milligrams for sessions 2 and 3, which is the targeted efficacious dose for the program. As this is a combination treatment of drug plus psychological intervention, it's important to understand both the dosing of the drug and the therapy component, which was informed by prior information in phase 2 studies.

In the phase 2 program, we evaluated

different study designs, including dose-response and low-dose controls to help address functional unblinding. We also tested different numbers of preparatory and integration psychotherapy visits. In phase 2, a greater mean reduction in CAPS-IV scores was observed in participants receiving three medication sessions compared to two with comparable safety. No further effect was observed in phase 2 participants receiving 4 to 6 medication sessions.

The time interval of at least 21 days between medication sessions allows for patients to process and integrate the outcomes of the prior medication session and sufficient time for three integration psychotherapy visits. These findings formed the basis for selection of the phase 3 design, which we developed in collaboration with FDA.

Let me describe the therapy environment and share what MDMA-assisted therapy entails. The therapeutic program was conducted utilizing a therapy manual that defined a patient-directed therapeutic method. The goal of the program is to

enable the patient to express and process what happened to them. The medication sessions took place in a small, comfortable room with a couch. Music was played during the session with soft lighting. At the start of the session, patients took 2 capsules; 1 and a half to 2 hours later, they took a third capsule.

The psychological intervention consists of alternating periods of time where patients engaged with the therapist or used eye shades to facilitate inner focus. Throughout the session, therapists continued to provide support and encouragement for staying present with difficult experiences and remind the patient to leverage stress coping techniques when needed. Successive treatment cycles help foster therapeutic alliance, which is important for patients to feel comfortable disclosing traumatic memories to their therapist. Overall, this allows for a personalized patient-directed therapy session.

Let me review the study personnel involved in these studies. There were multiple roles on the

study teams to deliver the combination treatment, as well as provide safety and quality oversight in these studies. The site physician and/or principal investigator were accountable for the conduct of the study and DEA license. In addition, they were responsible for eligibility determination and safety oversight.

Also, site therapists treated patients in preparatory and integration psychotherapy sessions and medication sessions. These were conducted similarly across all patients and standardized through therapist training. Therapists were not involved in any of the efficacy assessments. Sites often had multiple therapy teams.

Separate from site personnel, independent raters were trained and reliable to administer primary and key secondary endpoints and were blinded to the full study design, treatment assignment, and had communication restrictions with clinical sites. No rater assessed the same patient more than once on the CAPS-5.

Lastly, designated personnel provided

oversight for the study. Adherence raters reviewed and rated videos according to the treatment manual. Additionally, clinical supervisors reviewed videos and provided feedback to the therapists. Other qualified personnel oversaw efficacy and diagnostic assessments to ensure inter-rater reliability.

With that understanding, let me move to the study endpoints. The primary endpoint for both MAPP1 and MAPP2 was the change from baseline to week 18 in the clinician-administered PTSD scale, or CAPS-5, based on DSM 5 criteria. This tool is the industry standard for PTSD trials. A key secondary endpoint was the change from baseline to week 18 in functional impairment using the Sheehan Disability Scale, or SDS, across domains including family, social, and work life. The SDS is a 3-item, clinician-rated assessment of functional impairment associated with PTSD, rated on a 10-point scale, with 10 being maximum impairment.

The CAPS-5 total severity score is based on a 20-item clinical interview to assess a patient's PTSD diagnosis and symptom severity. The score is

clustered into four PTSD symptom domains. The CAPS-5 total severity score is calculated by summing severity scores across these domains, with each individual symptom rated on a scale ranging from 0, or absent, to 4, or extreme. Thus, a patient's CAPS-5 total severity score can range from 0 to 80, with higher scores indicating worse PTSD severity. A 10-point change on the CAPS-5 would typically enable a downward improvement in severity category and is considered clinically meaningful.

Functional unblinding is a known challenge in double-blind psychiatric clinical studies, especially if the drug has prominent psychoactive effects. I'd like to go into more detail to describe the measures we took to mitigate bias throughout our clinical program. First, the CAPS-5 is more objective than many patient-reported outcome measures. It is administered by a blinded independent rater who asks standardized questions about each PTSD symptom to elicit a detailed and largely behavioral description from the patient.

Additionally, the primary endpoint was assessed 6 to 8 weeks after the last medication session.

Patients were trained by the clinical sites to report their symptoms accurately and not disclose blinded information to the independent raters. The raters were also trained to detect under- and over-reporting of responses during the CAPS-5 assessment to reduce expectancy effect. All raters received training to achieve reliability at the beginning and throughout the study to maintain standardization of the assessments.

Raters were blinded to the study design, the treatment, and assessed each participant once. Raters conducted sessions remotely and were centralized. Accumulating efficacy data was kept in a limited access database. No site or sponsor personnel responsible for study conduct decisions had access to this database while the study was ongoing.

As noted earlier, the phase 3 design was conducted under a special protocol assessment developed in collaboration with FDA, which included

the statistical analysis plan. The prespecified statistical analyses are based on the modified intent-to-treat, or mITT, analysis population, which includes all patients who received at least one dose in one treatment cycle and had at least one CAPS-5 assessment.

The primary endpoint analysis uses a standard mixed model for repeated measures, or MMRM, with the de jure estimand to estimate the effect of MDMA on PTSD symptom severity in the intended patient population of PTSD. This estimand includes CAPS-5 assessment data of patients when adhering to their randomized treatment. To note, there was very little missing data in the phase 3 studies. Additionally, a prespecified sensitivity analysis included the use of the de facto estimand, which includes all CAPS-5 assessment data regardless of adherence to the patient's treatment program.

Now turning to study enrollment criteria, here are the key enrollment criteria used in both studies. MAPP1 enrolled patients with at least

severe PTSD symptoms, while MAPP2 enrolled patients with at least moderate PTSD symptoms to enroll a broader patient population. Most psychiatric comorbidities and some medical comorbidities were also allowed to support generalizability, and patients were required to have tapered antidepressants and other medications used off label to treat PTSD prior to dosing. Patients enrolled in both MAPP1 and MAPP2 generally reflect the current population of patients suffering from PTSD in the United States.

Now turning to the phase 3 results, in reviewing key baseline patient demographics across the pivotal studies, we see the average age was around 40 years. The majority of patients were female, which is generally reflective of the PTSD population. Patient PTSD characteristics were similar between treatment groups and studies, except for the baseline CAPS-5 scores. Patients experienced their PTSD on average for about 15 years. As you can see, this was a complex patient population with the majority having

multiple traumatic events and significant developmental trauma exposure.

There are only two FDA-approved treatments for PTSD. About one-quarter used sertraline, and 9 percent in MAPP1 and 2 percent in MAPP2 used paroxetine in their lifetime. Nearly all patients had received some type of psychotherapy. For MAPP1, CAPS-5 and SDS total scores demonstrate a population of patients with severe PTSD and functional impairment. For MAPP2, average CAPS-5 total severity scores were 5 points lower than MAPP1, consistent with moderate to severe PTSD.

To further highlight the complexity of this patient sample, shown here is the large burden of their psychiatric history. Over 90 percent of patients had experienced suicidal ideation in their lifetime and met criteria for major depression, with between 19 percent and 35 percent having previously attempted suicide. Overall, these diagnoses highlight the persistent, debilitating symptoms that negatively impact many aspects of a PTSD patient's life.

Moving to patient disposition from MAPP1, 91 patients were randomized -- 46 to MDMA and 45 to placebo -- with identical therapy. One patient withdrew consent prior to dosing in the placebo group. Forty-two patients assigned to MDMA and 37 receiving placebo completed the study. You can see that few patients discontinued.

Turning to the primary endpoint results, MAPP1 met the CAPS-5 primary endpoint. Patients assigned to MDMA had mean improvement from baseline of 24.5 compared to 12.6 on placebo, with a statistically significant difference from placebo of 11.86 favoring MDMA. Patients who received therapy with placebo also experienced clinically meaningful improvements in their PTSD symptoms, and the statistically significant difference between arms speaks to the added value of MDMA in this treatment paradigm. Looking at this endpoint overtime, MDMA quickly separated from placebo at week 7, and that effect was sustained through completion of the study.

Additionally, we assessed the clinical

relevance of the CAPS-5 reductions with various thresholds in a responder analysis. A greater proportion of patients assigned to MDMA achieved response, defined as greater than or equal to a 10-point reduction on the CAPS-5. After three sessions, more patients treated with MDMA did not meet clinical criteria for a PTSD diagnosis, defined as a treatment response and not meeting DSM-5 criteria, and more patients went into remission compared to placebo. Remission is the most stringent categorization of response, defined as patients being asymptomatic. These rates highlight the clinical relevance MDMA offers patients.

Moving to our key secondary endpoint, the SDS total score change from baseline was also met. Patients also experienced statistically significant improvement in functional outcomes. At week 18, MDMA patients demonstrated an improvement of 3.2 compared to 1.8 for placebo on a 10-point scale, with 10 being maximal impairment. Of note, 43 percent of the MDMA group and 14 percent of

placebo achieved mild impairment.

Turning now to MAPP2, which demonstrated consistent results to MAPP1, 104 patients were randomized in MAPP2, 53 to MDMA and 51 to placebo. Of note, one placebo patient was excluded from the mITT set because they did not provide outcome data. Overall, very few MDMA patients discontinued, with 98 percent of patients completing the study compared to 82 percent of placebo patients.

Moving to the endpoint results, MAPP2 also met the CAPS-5 primary efficacy endpoint replicating MAPP1. Patients assigned to MDMA had mean improvement from baseline of 23.7 compared to 14.8 on placebo, with statistically significant difference from placebo of 8.91; and here, you see this outcome overtime. MDMA separated from placebo at week 7, and that effect was sustained through completion of the study.

To highlight, despite the inclusion of patients with moderate PTSD symptom severity, MDMA demonstrated improvements across the three classifications in the responder analyses as

defined previously. For the key secondary endpoint, treatment with MDMA also demonstrated statistically significant functional improvement as measured by the SDS total score difference of 1.2 compared to placebo at week 18. Also, 56 percent of MDMA and 41 percent of placebo achieved mild impairment.

I'd like to finish with data from our long-term follow-up study, MPLONG. These data provide some evidence of durability, which may assist in evaluating the treatment effects observed in the acute treatment study. MPLONG is our observational study following patients from both MAPP1 and MAPP2. MPLONG was opened for enrollment approximately 7 months after the last medication session in MAPP1 and remained open throughout MAPP2. Thus, patients were unblinded from MAPP1 and remained blinded from MAPP2.

The study consists of 67 percent of patients from MAPP1 and 80 percent of patients from MAPP2. Patients resumed normal daily life, which included psychotherapy and medication, if needed, prior to

enrolling into MPLONG. This study features long-term follow-up among this subset of patients at least 6 months later with no additional study treatment. After at least 6 months, an additional CAPS-5 endpoint occurred, which represents a snapshot in time. As such, for today's presentation, I'll focus on the data from MAPP2 patients enrolled in MP LONG.

The subset of patients enrolled in MPLONG were generally consistent with the parent study. The average time of follow-up was approximately 10 months after the last medication session. Here's the data from those patients who entered into MPLONG from the MAPP2 parent study. The separation was maintained at their long-term follow-up visit, which was at least 6 months post last treatment.

These data suggest evidence of MDMA's durability to at least 6 months. Furthermore, a greater proportion of patients receiving MDMA achieved greater rates of response, loss of PTSD diagnosis, and remission compared to placebo.

Importantly, the MDMA rates are consistent since the week 18 visit in both MAPP1 and MAPP2 pivotal studies, demonstrating the clinically meaningful benefit of MDMA compared to placebo.

To summarize, MDMA-assisted therapy offers statistically significant and clinically meaningful improvement across two randomized, placebo-controlled clinical trials for the primary efficacy endpoint of CAPS-5 total severity score from baseline to week 18. Also, both studies met the key secondary efficacy endpoint. Separation in both CAPS-5 and SDS total scores with MDMA compared to placebo was seen following the first assessment and suggested evidence of durability compared to placebo. There was a greater proportion of patients in the MDMA group than in placebo who were classified as responders, loss of PTSD diagnosis, and those who achieved remission.

All sensitivity analyses support the conclusions from the primary and key secondary endpoints, and in totality, these results support MDMA in combination with psychological intervention

provides significant and meaningful reductions in PTSD symptoms and functional impairment in patients with PTSD. Thank you, and I will now invite Dr. Lilienstein to present the safety data.

Applicant Presentation - Alia Lilienstein

DR. LILIENSTEIN: Thank you, and good morning. I'm Dr. Alia Lilienstein, Senior Medical Director and Head of Clinical Science at Lykos Therapeutics. I'm the clinical lead for the MDMA program. I'm a board certified family medicine physician. In my practice, I often supported patients with PTSD and their families. I witnessed the immense suffering PTSD inflicts on the patient, not just psychological but also physical. I joined this research effort seven years ago to help advance the science so that my patients might have new effective treatment options.

As stated previously, MDMA is not a new drug. It has been studied since its discovery in the early 1900s. This extensive body of data, including exposure in more than 2,000 people in clinical trials, has informed the clinical

development program for PTSD. In fact, our initial IND was phase 2 enabling because the safety profile of MDMA was already well documented from this initial body of evidence. The safety database includes one study conducted by NIDA and 17 sponsor-conducted studies in more than 400 participants. Of these, 287 patients with PTSD have received MDMA.

As this application is for an acute treatment of a serious and life-threatening condition with high unmet need, the size of the safety database is consistent with FDA guidance for acute treatments and should be sufficient to ensure safe use under the proposed conditions.

Today's presentation will focus on the pooled safety data from the two pivotal phase 3 studies. The overall safety profile observed in our program aligns closely with what has been previously described about key safety issues associated with MDMA as seen in the literature and other studies.

Now focusing on the two pivotal phase 3

studies, in the pooled phase 3 studies, most patients received the intended dosing regimen for each treatment cycle. In cycles 2 and 3, only 2 percent and 3 percent did not receive the escalated first part of the split dose. Within each treatment cycle, 92 to 97 percent of patients received the second part of the split dose.

Now turning to the overall safety profile, MDMA was well tolerated with mostly transient mild to moderate adverse events. Nearly all patients irrespective of group experienced an adverse event with severe events being comparable between the two groups. The proportion of serious adverse events and adverse events leading to study discontinuation was low, with only one MDMA-treated patient discontinuing due to an AE and no MDMA patients experienced a serious adverse event in the phase 3 program. Lastly, no deaths were reported in the pooled phase 3 studies.

Here are the most common adverse events occurring in at least 15 percent of patients. Overall, the imbalances in adverse events were

within expectation and consistent with the known mechanism of action for MDMA. For example, muscle tightness, decreased appetite, nausea, and hyperhidrosis have all been reported in the literature. Most events were self-limited, and most related adverse events resolved within 2 days.

Now, I will discuss the key observed and potential risks based on what was reported in the clinical development program and seen in the literature. We know MDMA is associated with neuropsychological effects that result in temporary alterations in perception, mental state, cognition, and sensation, and may increase feelings of empathy, openness, and social connectedness, and decreases in sensitivity to negative emotions such as fear or anger. These acute effects are thought to be a central component of its long-term treatment benefit, and this altered mental state may result in patient impairment.

These subjective effects of MDMA are well characterized in the published literature and are reflective of the mechanism of action of the drug.

As noted in the briefing documents, we did not collect positive or neutral effects of treatment in our phase 3 trials, as we interpreted adverse events to mean negative events. We acknowledge this limitation, and we are prepared to collect and evaluate the subjective effects postmarketing to better inform the understanding of how they may contribute to patient impairment and its risks.

In addition to the neuropsychological effects, MDMA causes physiologic effects, with dizziness being the most common. In our phase 3 clinical trials, we took several measures to mitigate risks related to neuropsychological and physiologic effects. Patients had preparatory therapy sessions prior to any MDMA medication sessions in order to establish a good therapeutic rapport. Patients were cared for by licensed and trained therapists who are present throughout the medication sessions. Patients were given support as needed during their medication sessions, such as help getting up from a seated position and were required to have someone available to drive them

home.

As described earlier, this is a vulnerable patient population with comorbid psychiatric symptoms, including suicidal thoughts and feelings. Furthermore, MDMA may catalyze therapy and allow for more intense processing of thoughts and feelings; therefore, the clinical trials were designed to assess for emergence or exacerbation of suicidality. Patients were excluded from the studies if there was an imminent serious suicide risk or if they were likely to be re-exposed to their index trauma or other significant trauma during the study.

Patients with active suicidality were included, and suicidality was assessed frequently by administration of the Columbia Suicide Severity Rating Scale, or C-SSRS, which is the standard tool for suicide risk assessment. This was done to ensure a thorough understanding of participants' suicidality was reflected in the data, including an assessment of lifetime suicidality during screening.

In the phase 3 studies, both treatment groups reported a high incidence of any suicidal ideation in their lifetimes, 87 percent in the MDMA group and 88 percent in the placebo group. Of those, 35 and 37 percent reported serious suicidal ideation in their lifetimes. Additionally, 27 and 31 percent reported lifetime suicidal behavior.

Here are the AEs reported that reflect suicidality. These include any C-SSRS scores greater than baseline, as well as any worsening reported by the investigator. Patients in both groups experienced suicidal symptoms, which are expected in this patient population. The frequency of symptoms was comparable between the two groups. Of note, there were no suicidal behaviors or attempts reported in the MDMA group.

MDMA has some pathomimetic effects and is known to increase blood pressure and heart rate in a dose-dependent manner. Patients with moderate risk factors underwent additional screening, including cardiac stress test. Such patients included those with well-controlled hypertension or

diabetes, even if they had no known prior cardiovascular disease. Patients were excluded if they had underlying medical conditions, which may place them at excess risk due to these effects. For example, patients were excluded if they had uncontrolled hypertension, significant cardiovascular or cerebral vascular disease such as a history of a heart attack or stroke, and atrial and ventricular tachyarrhythmias. Vital signs were measured at the medication sessions prior to dosing at an interim time point during anticipated peak effects of the drug and at the end of the session.

Here you see systolic blood pressure on the top and diastolic blood pressure on the bottom over each treatment cycle. We see that the mean blood pressures increased from pre-dose at the interim time point and returned to pre-dose levels by the end of the sessions, with higher elevations at the higher doses in treatment cycles 2 and 3. No antihypertensive treatments were reported to have been administered in response to these elevations. Also, these elevations did not result in adverse

clinical outcomes such as heart attack or stroke, and no patient discontinued therapy due to these changes.

Looking at systolic and diastolic blood pressure by threshold increases rather than by means, only 1 to 3 percent of patients reported systolic elevations greater than or equal to 180, and 1 to 3 percent reported diastolic elevations greater than or equal to 110.

Now, for mean heart rates, heart rate also increased at the interim timepoints with higher elevations at the higher doses and remained slightly elevated about 11 beats per minute higher at the ends of the session. Heart rates generally were at pre-dose levels by the next vital sign measurement.

Here you see box and whiskers plots for rate pressure product by medication session. Rate pressure product is the product of heart rate times blood pressure. It estimates myocardial oxygen consumption and can be used to assess the risk of cardiovascular events. To put these results in

context, the upper bound of the Y-axis represents the typical rate pressure product achieved in a cardiac stress test. The median rate pressure product and all outlier patients at the interim timepoint were below the stress test level.

Here is the rate pressure product summarized by the maximum value for each patient at the interim timepoint across the three sessions. Again, we see that no patients had a rate pressure product greater than what is achieved in a cardiac stress test. Four MDMA-treated patients experienced intermediate response and most patients had low intermediate response or less.

MDMA has moderately high potential for abuse. Importantly, however, illicit MDMA use is known to be primarily episodic and rarely results in substance-use disorders. That is likely because MDMA is primarily serotonergic in action and is unlikely to produce physical dependence or withdrawal syndrome. This distinguishes it from typical psychostimulants, which primarily activate the dopamine system.

The morbidity and mortality associated with illicit MDMA is considerably lower than methamphetamines, similar to amphetamines, and higher than methylphenidate. While use of illicit MDMA cannot be completely prevented, approval of a controlled product provides the opportunity to regulate and monitor the field to a greater extent than what is currently possible.

We're working with the FDA to develop a REMS program to evaluate and mitigate the risk of serious harm resulting from patient impairment. According to the proposed REMS, MDMA will only be dispensed in certified healthcare settings and only with evidence of safe-use conditions. This includes training for prescribers, pharmacists, and therapists, and patients will be counseled to support safe use. Patients will be monitored during and after the session and will be required to be enrolled in the midomafetamine drug registry.

Beyond the REMS, we're working with the agency to develop a comprehensive plan to mitigate risk and translate the positive benefit-risk of

MDMA-assisted therapy observed in the clinical trial setting to clinical care post-approval. The mitigation efforts address each of the identified or potential risks. They include patient monitoring; appropriate labeling; prescriber educating, including appropriate selection of patients; and therapist training on patient monitoring for these risks.

We also have additional efforts to support use in clinical practice. We plan to initially work with a limited number of sites that takes specific steps to put the staff and processes in place to effectively and safely deliver MDMA-assisted therapy. The basic premise of this treatment approach is that the psychological component is important.

To support MDMA use in clinical practice, we will provide training for therapists on the treatment approach used in the phase 3 clinical trials. Furthermore, the medication for this acute treatment will be supplied in single-dose packaging, further limiting non-medical use and

medication errors.

To conclude, overall, three total doses of MDMA were well tolerated. The adverse events were consistent with the known safety profile of MDMA with mostly mild to moderate and transient adverse events. No patients assigned MDMA died or experienced a serious adverse event in our pivotal studies. In addition, key risks can be appropriately managed and mitigated with the proposed labeling and REMS. The favorable safety profile observed in the clinical program will translate to practice if approved due to the inherent safeguards of an acute treatment with controlled distribution.

Lastly, we agree with the agency that additional postmarketing studies such as laboratory safety data collection can further inform patients and providers. While the benefit-risk of this treatment is well characterized by our clinical development program, we recognize more can be learned in the real-world setting. We acknowledge the need to move forward with care and caution to

bring this new tool to patients suffering from this serious and life-threatening condition.

Thank you, and I'll now turn the presentation to Dr. O'Donnell to share her clinical perspective.

Applicant Presentation - Kelley O'Donnell

DR. O'DONNELL: Thank you. I'm Kelley O'Donnell. I am a board certified psychiatrist and Research Assistant Professor of Psychiatry at the NYU Grossman School of Medicine. In addition to providing conventional treatment to patients with PTSD, I worked as a study physician and therapist on both of the phase 3 trials that you've heard about today, so I appreciate my opportunity to offer a clinical perspective on the data.

When I was in medical training, I only learned about the potential harms of drugs like MDMA, so I was surprised when I first heard that it was being studied as a potential treatment for PTSD. But then with further investigation, I learned about the early use of MDMA in a clinical setting where its acute subjective effects were

used to catalyze psychotherapy. And then as the phase 2 data started coming out, I started to get very interested because, as you've heard, so many people with PTSD are really suffering, and that unmet need has enormous consequences.

PTSD is associated with a significantly increased risk of mortality, driven by medical and psychiatric comorbidities, as well as an increased risk of suicide, and there are treatments available for PTSD, but they're insufficient. The FDA-approved medications are associated with low to moderate efficacy and they're not disease modifying. In the community, patients are often prescribed several medications for off-label treatment with different drugs targeting different symptoms, and this of course subjects them to the risks associated with polypharmacy.

Patients are also in need of more options for psychotherapy. Evidence-based interventions are associated with high dropout rates for patients able to access them, and we generally don't think of psychotherapy as a rapid-acting treatment for

PTSD. One challenge in trauma treatment is that the therapeutic processing of traumatic memories can only happen when a patient feels safe, but many patients with PTSD move through the world feeling fundamentally unsafe in their own bodies and in relationship with others, so a therapist often has to spend many months, if not years, establishing and strengthening the therapeutic relationship before engaging in any trauma-focused work; and these are all reasons why it's been so rewarding to see how quickly and meaningfully patients improve with MDMA-assisted therapy.

This combination treatment of MDMA-assisted therapy is well named because the acute drug effects of MDMA really do assist the therapeutic process itself. First, MDMA often generates an increased sense of empathy and connectedness within oneself and with others. Although it's important to establish rapport before the medication session, MDMA may further foster the patient's sense of safety and trust in themselves and in the therapist. MDMA also appears to increase recall of

affectively charged memories such that more content may become available for processing, which can happen during and after the medication sessions.

Finally, the serotonergic effects of MDMA often lead to transiently reduced anxiety. This is important because it's not uncommon for patients to actively revisit their trauma during the medication sessions and experience intense emotional and somatic expression. That somatic expression might be important for targeting the core pathology of PTSD, but it can be highly aversive in ordinary states of consciousness. But with the MDMA on board and the attendant reduction in anxiety, there's often a greater ability to stay with and process the memories and emotions rather than dissociating or becoming emotionally dysregulated.

Patients have often described trauma-related insights, increased self-compassion, and these things can persist long after the acute drug effects have worn off. All of these experiences during the medication session can then be recalled, elaborated, and consolidated during the drug-free

therapy sessions.

I saw some phase 3 participants visibly brighten over the course of treatment, with better sleep, reduced physiologic symptoms, improved sense of self-worth, better emotion regulation; and what I thought was really most powerful to see was a greater ability to pursue goals and engage in meaningful relationships in a way that it previously felt impossible.

Other participants I saw who had residual symptoms after the three treatment cycles, several reported that they continued processing their trauma in conventional psychotherapy and that they were doing so more effectively than they'd been able to do before the treatment because their overall sense of safety, trust, and self-efficacy was higher.

This treatment is under a lot of scrutiny right now. PTSD patients are a genuinely vulnerable population, and some of the strengths of MDMA may also represent challenges moving forward. Careful screening, education, and monitoring of

patients, and the rigorous training of licensed healthcare providers, will be essential for mitigating those risks. But the complexity of this treatment, like the complexity of the PTSD population, should not preclude approval because it's clear that MDMA-assisted therapy would be a welcome addition to the available options.

I've seen firsthand how this intensive treatment can be life saving for some, including some who haven't benefited from conventional approaches at all, and this need is, of course, all the more urgent because despite the seriousness of this disease, we haven't seen a new pharmacologic intervention for PTSD in decades.

In this combination treatment, the acute effects of MDMA facilitate the psychotherapy, strengthening the therapeutic alliance, facilitating the patient's development of insights and tools they can continue to cultivate long after the acute effects have worn off, and I think patients will especially value the fact that this is an acute treatment, about 12 weeks, and that

there's the potential for a durable response.

I look forward to being better able to support my patients and those who care for them with this valuable and urgently needed treatment option for PTSD. I appreciate your time and attention. I'll now return the presentation to Dr. Yazar-Klosinski.

Applicant Presentation - Berra Yazar-Klosinski

DR. YAZAR-KLOSINSKI: Thank you, Dr. O'Donnell.

I'll now summarize the benefit-risk. MDMA-assisted therapy offers statistically significant and clinically meaningful improvement in PTSD symptoms and functional impairment compared to placebo across two phase 3 trials with evidence of durability over time. This is a novel combination of limited exposure to drug which catalyzes psychological intervention. The adverse events experienced are as expected for MDMA and were mostly mild and self-limited. The careful screening and monitoring of prospective patients and the selection and rigorous training of

therapists will be essential for mitigating risks. A staged and controlled rollout will help to ensure high-quality implementation.

Overall, given the efficacy and safety data you've heard about today and the substantial unmet medical need for treatment of a serious and life-threatening disorder, MDMA in combination with psychological intervention provides an effective, well tolerated acute treatment for PTSD. Thank you, and we will now take your questions.

Clarifying Questions to Applicant

DR. NARENDRAN: We will now take clarifying questions to Lykos Therapeutics. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up questions with, "That is all I have for my questions," so we can move on to the next panel

member.

For our panel members joining us virtually, please use the raise-hand icon in Zoom to indicate that you have a question and we will acknowledge you. Please remember to lower your hand by clicking the raise-hand icon again and after you have asked your question.

We'll take clarifying questions for Lykos Therapeutics. Our first questions from Dr. Dunn.

DR. DUNN: This is Walter Dunn. Before I ask my question, I actually would like to thank the agency for holding this meeting in person. I think the conversation will be that much more fruitful, and then it's also good to see colleagues in person.

So let's start with two questions. The first question is perhaps for Ms. Laverdiere. My question is regarding the psychotherapeutic component of the treatment. Obviously, this is going to be a major part of our discussions today. My question is regarding the role of the psychotherapy as far as risk mitigation.

Based off the sponsor's presentation, it appears that the psychotherapy is perhaps the driving force of the efficacy seen in MDMA-AT, but I wanted to get your opinion on what you believe or propose to be the the safety aspect of your particular psychotherapeutic model. So, for example, page 29 of of your briefing document, you list out how your psychotherapy and therapeutic elements in the psychotherapy, most of it's spontaneous, whereas more traditional trauma-focused therapies tend to be more directive.

Is there any reason to believe that using a more directive, manualized approach would be any less safe when using conjunction with MDMA?

DR. YAZAR-KLOSINSKI: We also see the psychotherapy component as an important risk mitigation factor. For example, if there are affective memories that are recalled that may cause distress, the healthcare providers are available to encourage the use of stress coping techniques.

I'd like to invite Dr. Kelley O'Donnell to speak to her clinical experience on that point.

DR. O'DONNELL: Kelley O'Donnell. It's a really interesting and important question. I think the kind of psychological support that was offered during the actual MDMA sessions themselves was informed by that first wave of research with MDMA. So again, a lot of the traumatic material is coming up spontaneously, so the therapists are really trying to maintain a present focus and one that's directed by the patient, what's coming up for them in that moment and how can the therapist help them feel into that experience rather than avoiding it or suppressing it, so really helping them take advantage of the fact that the MDMA is on board.

That being said, I think that over the next several years, we're going to find that other psychotherapies can also take advantage of these different effects. I know that there are already certain investigator initiated trials that are looking at different kinds of psychotherapy in conjunction with MDMA for different clinical indications. I think there are certain basic aspects regarding safety like you're pointing to in

terms of are they creating an appropriate holding environment for there to be able to be safe processing of these intense emotions that might be coming up or are these new traumatic experiences that they might become aware of, but that I think also is something that could be incorporated into a different kind of training.

DR. DUNN: Great. Thank you.

The second question, there was a recent, fairly high-profile ISA review with claims that there was misconduct during the clinical trials. Lykos responded fairly quickly to that with a public letter. My question is, number one, when was Lykos first made aware of these allegations, and number 2, what steps did Lykos take to investigate and rule out that these things didn't occur? As your letter indicated, there wasn't any denial of such misconduct. Did you do an internal investigation? Did you hire a third-party law firm to come in to investigate? Can you speak to that?

DR. YAZAR-KLOSINSKI: I'd like to invite Dr. Lilienstein to speak to this.

DR. LILIENSTEIN: Dr. Lilienstein, Lykos Therapeutics. The company was initially made aware of this event in late 2018 and investigation was undertaken internally in the company to both understand what had happened and improve any processes within the company to prevent this in the future.

It's never ok for a care provider to cross boundaries. It's unethical behavior and it's malpractice. We work with licensed and healthcare providers now only, and they are trained, in addition through our therapy training program, to understand how the drug may impact boundary setting for patients and to reinforce an upholding of boundaries on their part of things as well.

DR. DUNN: So in addition to the boundary violation -- I think that's going to be a big part of the conversation a little bit later on -- there were allegations that some folks, or some subjects, were discouraged from participating in MPLONG. And based off of your briefing document, it appears that patients either were enrolled in MPLONG or by

themselves decided not to. There was no suggestion that they were excluded by the principal investigators but, again, allegations from the recent ISA review suggesting, again, unsubstantiated claims of subjects stating that they were discouraged from participating in the long-term durability study.

Were those things investigated?

DR. LILIENSTEIN: Yes, those were investigated as well, and all participants who were interested in participating were given the opportunity to review consent, and some chose not to participate after reviewing consent; but otherwise, everyone was given the opportunity.

DR. DUNN: So my understanding is that no subjects were excluded based off of one of the second criteria, which was if there are any problems that the principal investigator identified, that would make participation in MPLONG problematic.

DR. LILIENSTEIN: There was at least one participant, I'm aware of, who because they were

doing so poorly, felt like their participation in the study would be really negatively impacting for them, but a conversation was had.

DR. DUNN: Okay. Thank you.

DR. NARENDRAN: Our next question is from our virtual member, Dr. Holtzheimer.

DR. HOLTZHEIMER: Thank you. Paul Holtzheimer, National Center for PTSD. My question also relates to the psychotherapy element, a two-part question. What measures or assessments did you do to investigate the integrity and quality of the psychotherapy provided in each study arm, and what data do you have to support that there were or were not, importantly, any systematic differences in the psychotherapy provided in the two arms?

DR. YAZAR-KLOSINSKI: The treatment manual for MDMA-assisted therapy was finalized in 2017 for the phase 3 program. In addition to this, there was an adherence rating manual developed, which included specific criteria for the three types of therapy sessions. These include preparatory

psychotherapy, medication sessions, and integrative psychotherapy sessions.

We had blinded adherence raters that reviewed videos and rated on a dichotomous scale whether these specific criteria were adhered to, and in terms of the quality, there was a clinical supervision process where master clinicians also reviewed videos and gave feedback to the therapists delivering MDMA-assisted therapy. What we saw, ultimately, is that the therapy was highly standardized during the medication sessions between groups.

DR. HOLTZHEIMER: And to be clear, those adherence measures were done during the phase 3 trials?

DR. YAZAR-KLOSINSKI: That's correct.

DR. HOLTZHEIMER: Thank you.

DR. NARENDRAN: Our next question is from Ms. Witczak.

MS. WITCZAK: Good morning. Kim Witczak, consumer rep. I guess mine goes along the lines of the psychotherapy. Is that a proprietary

therapeutic manual that will be required? Because, obviously, we didn't test it against other therapy psychotherapy. So is that proprietary to you? Because I know there are other investigational clinical trials going on out there right now that will have their standards. So that's one question.

Then in terms of harms -- and I guess it goes around the relational harms and suggestibility. Also, there's like a pro movement and there's a lot of emphasis on this psychedelic, which I am happy to see, but how did that influence when -- I know the criteria, people wanting to see it, how much did that take into consideration with your efficacy?

And that might be something even for the FDA to answer later, but I think the first two are really about is it proprietary to you and all the people having to go through training -- and it has to be your model because, obviously, MDMA is something that you buy on the street, and it's out in the clubs, and it's the love drug -- and then how does relational harms and suggestibility

handle? Because you didn't look at euphoria, I'm curious about that. Thank you.

DR. YAZAR-KLOSINSKI: The therapeutic method is not proprietary to us. In fact, the treatment manual was made available since 2017, or earlier in fact, to therapists so that they could better understand the types of methods and how they might incorporate certain aspects of standardized and well-utilized standard of care psychotherapies.

That's one of the reasons we selected "psychological intervention" as the term for that component of the intervention, so that it can hopefully be broader and encompass a variety of methods. What we will do, though, is train the therapists in how the therapeutic method was delivered in the phase 3 trials so they can have an understanding of what was done as the basis of the safety and efficacy.

In terms of the relational harms, certainly this one case of misconduct we just spoke about would negatively impact therapeutic alliance, so I'd love to invite Dr. O'Donnell to speak to how

relational harm may impact the delivery of the psychotherapy.

DR. O'DONNELL: Thank you. Kelley O'Donnell, psychiatrist. As you point out, the very things that can cause relational harms in some ways are the very aspects that may also be therapeutic in this treatment. In the training, we talk a lot about that fact; what are the subjective effects and how does that make the patient more vulnerable? How does that shift the power dynamics between the patient and the provider? Those power dynamics are at play in any healthcare relationship, and yet, in a trauma-centered approach, we really work to empower the patient to be the source of their own healing process.

So it's something that we talk about a lot. We think a lot about how are we -- and this gets to your question, I think, a little bit about expectancy bias -- priming the patient to look for a particular result, to hope for a particular result? That's something that I think about as a therapist, even without MDMA or any other

substances on board. But again, MDMA is really amplifying those kinds of concerns.

So it's one reason why I think it's so important that the training goes beyond the manual. There's the manual, but then there's also a lot of didactic components, a lot of Q&As with people who have experience in the modality, and then I think most crucially is the supervision that happens afterwards.

So much as we don't expect that someone who just graduated from medical school, has their MD, is ready to take care of our grandparents, they require a period of clinical supervision. And it's in that period that we really learn what all of these things mean, what vulnerability looks like, what really is at stake, and how am I as a therapist exacerbating or mitigating those potential harms?

So I think that it's really important for the education to be comprehensive to go beyond merely what a pharmaceutical company can do and extend into a much bigger professional community

conversation around all of these things, how codes of ethics really do. We need to change, we adhere to, and for people to be accountable to them along the way.

DR. NARENDRAN: Our next question is from Dr. Joniak-Grant.

DR. JONIAK-GRANT: Thank you. Dr. Joniak-Grant. So I am here today as the patient representative, and as we're talking about harms and issues with therapy, the first thing I would like to mention is let's try to not gloss over this misconduct. It was sexual misconduct. That's particularly important, as individuals that have PTSD are most likely to have sexual violence. So I think it's important that we not try to just say, "Oh, misconduct." It was more than that.

Moving on from that to my question, I wanted to ask a little bit about inclusion and exclusion criteria. In reading through the materials, it said that people were included in the study if they had up to 10 prior uses of MDMA, and I would like to know what percentage of clinical trial

participants in the phase 3 trials previously used MDMA and is there data for how many times individuals were using it? Was it some people used it once, some people used it twice, lots of people used it 8 times? I think that information is really important because there could be a self-selection bias at play.

There also was an inclusion criteria that the participants needed to agree to specific lifestyle modifications. I would like to know what this means, and then finally, how were participants recruited? Thank you.

DR. YAZAR-KLOSINSKI: Alright. So I'll take your question in three parts. On the topic of prior use of MDMA, I'll bring up a slide that shows the percentage of participants from MAPP1 and MAPP2 from the pooled phase 3 studies who had a history of illicit MDMA use. This was balanced between the groups. And we also were curious about whether this might have an effect on the results, so we conducted an analysis to determine if that might have had an effect, so perhaps our team can bring

that up. Here we go.

When we look at participants with any history of MDMA use versus those who did not have any history of MDMA use, we didn't see a difference in the treatment outcomes. As you can see, the results still favor MDMA regardless of that history; and we certainly acknowledge that was a thought for us, too, on whether that might pose a confound, but it did not appear to in the end.

In terms of lifestyle modifications, I'll have to check with our team to see if we have a slide, but essentially, these studies, they consist of about 19 visits. On the days of the medication sessions, there were 8 hours of medication session, and in addition, participants had to agree to fast prior to the medication session. At the time of the phase 3 study being designed, we had not yet conducted our food effect study, which ultimately found that dosing can happen without regard to food, so light breakfast would have been fine.

In addition to that, the participants had to agree to regular follow-ups with the study team, so

after the medication session, there were very frequent phone calls for 2 weeks following each medication session, so they had to agree to be available for those phone calls. So hopefully that gives you an idea of the types of lifestyle modifications intended there.

In terms of recruitment, we used standard methods for recruitment. We had a recruitment website. This captured inquiries from the internet. And then with zip code matching, we enabled clinical trial sites in that geographic location to follow up directly with the participants so that any concern over self-selecting into the study would also further be addressed by accepting recruitment from referrals from other clinicians that were already treating PTSD patients.

DR. JONIAK-GRANT: So just to follow up on recruitment, you said that there was a website. How did potential participants know this website existed? How was awareness raised? I help design recruitment. You said there's a standardized

approach; there's really not, so I'd like to know more specifics, if possible.

DR. YAZAR-KLOSINSKI: I'll invite Dr. Lilienstein to speak to that, as she was involved in running the studies.

DR. LILIENSTEIN: Dr. Lilienstein, Lykos Therapeutics. A lot of recruitment for the sites came from the PTSD networks in the area. We had clinical trial sites all throughout the U.S., and Canada, and Israel, and they were connected to other VA hospitals and PTSD locations, so there was a lot of recruitment from referrals. But the website was distributed through the sponsor's network and then through investigators' networks as well.

DR. JONIAK-GRANT: Thank you.

A follow-up on that, I also asked if there was any data on the prior use, how many times they had used MDMA in the past?

DR. YAZAR-KLOSINSKI: We did have certain restrictions on how many times, total, would be allowed in the study. Within those guardrails,

what we saw was 1 to 2 times on average.

DR. JONIAK-GRANT: Okay, but no actual data.

DR. YAZAR-KLOSINSKI: That's something we'll be able to get you after the break.

DR. JONIAK-GRANT: Thank you.

Then just a follow-up question; why did participants choose to discontinue treatment or withdraw from the MDMA arm of the study? There's one call-out of someone who had depression, and the other participants who withdrew or discontinued treatment, the reasons for it were not mentioned, and are they known?

DR. YAZAR-KLOSINSKI: Yes, they're certainly known. Here's a slide that summarizes the primary reason for early termination and dropout across the two phase 3 studies and pooled. We did conduct the MAPP1 study concurrent with the COVID pandemic, so that did influence the results a little bit, but it was balanced between groups, as one would expect from standard principles of randomization.

In terms of the adverse events, one MDMA participant discontinued due to depression, and in

MAPP2, which did have very good retention, 98 percent in the MAPP2 of the MDMA group had completed the study, but that one person that dropped out actually completed all three medication sessions, and they expressed that they were not willing to complete the CAPS-5 assessment because it was perceived as activating their PTSD symptoms.

DR. JONIAK-GRANT: Okay, but I see up there, withdrawal of consent. Any information about why that participant withdrew their consent? That's what I'm trying to understand.

DR. YAZAR-KLOSINSKI: I understand.

Dr. Lilienstein, can you please speak to that?

DR. LILIENSTEIN: I think we'll have to get that specific information for you after the break. I'm sorry. I don't have it at this time.

DR. JONIAK-GRANT: That's ok. Thank you.

DR. NARENDRAN: Next question is from Dr. Hertig.

DR. HERTIG: John Hertig, member of DSaRM. I have a two-part question. The first is related

to the controlled distribution pathway, and I think I want a little bit more detail on, if I'm a patient, how am I obtaining the medicine or the controlled substance, and then how is it being administered? So that's the first question, walking me through that control distribution pathway.

Then the second is under the mitigation strategies. There was a mention of limited rollout, so can you walk me through what limited rollout means and what metrics of success you would use to then expand access, please? Thank you.

DR. YAZAR-KLOSINSKI: Based on the parameters of the proposed REMS, which we're still developing with input from FDA, the dispensation would only take place in certified healthcare settings that also have demonstrated evidence of safe-use conditions. So by controlled distribution, what we mean is that there would be a limited number of pharmacies. They would either have to be on site at the certified healthcare setting or similar type of distribution approach.

There are additional restrictions on compounds that are dependent on their ultimate scheduling by DEA, so there are still some details that need to be worked out in terms of what is completely compliant with both FDA expectations and DEA regulations, and that's something we're actively engaged and working on with both FDA and DEA; so it's something that we'll follow all the requirements that apply, depending on how the scheduling goes.

In terms of how the product is administered, this would only be administered in these certified healthcare settings that have the appropriate personnel and plans in place to conduct the patient monitoring, deliver the psychological intervention, and also have plans in place for medical escalation. And in terms of the limited rollout, what we intended is that we would start out with a smaller number of commercial sites that we're able to meet the requirements of this certified healthcare setting with safe-use conditions in order to essentially pilot what our risk mitigation

procedures are able to detect, and submit reports to the agency for those REMS assessments on the required schedule.

The metrics for how we would expand upon patient access are something that we're also still developing; however, we strongly believe that patient access is very important, and as a result, we're envisioning this as a staged rollout. So although we may start with a limited number of sites initially, after demonstration of appropriate risk mitigation, we would plan to expand from there.

DR. HERTIG: Thank you. So just as a follow-up, in knowing that the REMS program and logistics still need to be worked out a little bit, it would be feasible or possible in the sponsor's mind that you would go to one of these pharmacies, get dispensed one dose, and then take that with you to the therapy session; is that correct?

DR. YAZAR-KLOSINSKI: The dispensation would have to happen at the certified healthcare setting that would be also the same location where the --

DR. HERTIG: So it would have to be an on-site location.

DR. YAZAR-KLOSINSKI: Correct.

DR. HERTIG: Thank you.

DR. NARENDRAN: Our next question is from our virtual panel member, Dr. Barone.

DR. BARONE: Hi. Good morning. Melissa Barone, VA Maryland Health Care System. I have two questions about the adverse events that were reported. One, on page 88, it mentions that there are a couple of people in both the treatment group and the placebo group that have reported non-suicidal self-injury, and I was wondering if that happened within the context of being under the influence of MDMA, or immediately afterwards, or later on after the medication session.

My second question is, you were tracking how many of the participants had a substance-use disorder and alcohol-use disorder, and I was wondering was that part of the adverse events that you tracked, relapses or active use, while they were enrolled in the study.

DR. YAZAR-KLOSINSKI: Dr. Lilienstein will speak to this.

DR. LILIENSTEIN: Hi. Dr. Lilienstein, Lykos Therapeutics. Regarding self-injury, those AEs were not during MDMA sessions or close proximal time to MDMA sessions. About alcohol-use disorder and cannabis-use disorder, mild disorders were allowed in the study or moderate and early remission, and there are no relapses in the AEs.

DR. BARONE: Thank you.

DR. NARENDRAN: Our next question is from Dr. Amirshahi.

DR. AMIRSHAHI: Hi. Maryann Amirshahi. I actually have two questions. One is safety and one is about access. One of the things that you pointed out was that 46 percent of your patients with PTSD have substance-use disorder and 40 percent of them you said had also used MDMA illicitly prior to the study. So my question for you is, it doesn't seem that we evaluated if they went on to use illicit MDMA after the fact, and how these therapy sessions -- by introducing somebody

that already has SUD or is at high risk of SUD in multiple sessions using MDMA, why didn't we follow up to see if there was a subsequent uptick in illicit use?

The reason I say that as a medical toxicologist is we're actually managing more and more severe cases of MDMA overdose, so I'm less concerned about the safety in the acute setting, but more chronically, if they go on to abuse MDMA, that drug is much less safe on the street.

My second question is regarding access. You mentioned all of the safety protocols that you have in place, and it seems as though -- and bear with me if I'm misspeaking -- some patients may require an echo. This may be an 8-hour therapy session. This medication is intended to be approved with therapy, but at the same time, we say that a lot of patients don't have access to therapy.

So what are your steps? Moving forward, what is your plan to do, perhaps, cost effectiveness analysis and to help make sure that patients who may have coverage for drug will also

have coverage for this, as part of ensuring access in a vulnerable population? Thank you.

DR. YAZAR-KLOSINSKI: I'll take this question in three parts, the first being the safety procedures, which I'll invite Dr. Lilienstein to speak to, followed by the question around access to therapy and our cost effectiveness analyses.

Dr. Lilienstein?

DR. LILIENSTEIN: Hi. Again, Dr. Lilienstein, Lykos Therapeutics. For use of illicit MDMA and conversion to illicit use after exposure to MDMA in a treatment setting, we didn't have any adverse events in our phase 3 clinical trials of patients during those trials and during the 8-week follow-up period after the last medication session of anyone using illicit MDMA. We did assess an MPLONG or a long-term follow-up study as to whether patients had used illicit MDMA in the interim time period, and some participants did use illicit MDMA. As a reminder, some participants had used illicit MDMA previously, though.

I'm going to bring up a slide for you that shows you the percentage of people who used it and who had used it previously. There were 13 MDMA participants who had used ecstasy previously and went on to use ecstasy -- sorry; six of those were previously and went on to use ecstasy in the future. So we have 7 people who had never used it before, and after our study, went on to use MDMA; and of the placebo, the 7 people who went on to use it had all had a history before.

We did ask them why they chose to use illicit MDMA -- which is the next slide I'll bring up for you -- and again, the vast majority of people did not use, but for people who did use MDMA, people were using it for treatment of a mental health condition, personal growth, with a very small amount for recreation. And most importantly, no one used MDMA to satisfy a craving.

DR. YAZAR-KLOSINSKI: Thank you, Dr. Lilienstein.

In terms our goals for enabling access to therapy, we have already started to collaborate

with other companies. That has resulted in an insurance code being issued by the AMA, and it's actually been in use for part of this year already. We do have a cost effectiveness analysis modeling plan, and we are taking into account not just the cost of the drug but also the psychological intervention in that model. It's not something that is available yet to the public, but it is something we're currently working on and prioritizing.

DR. AMIRSHAHI: Thank you.

DR. NARENDRAN: The next question is from Dr. Rebo.

DR. REBO: Hey. Elizabeth Rebo. I was wondering if you could expand upon your plan for postmarketing lab monitoring, specifically with LFTs and others, since there's limited information from your phase 3 studies.

DR. YAZAR-KLOSINSKI: I'd like to invite Dr. Lilienstein to speak to this.

DR. LILIENSTEIN: Hi. We recognize that the LFTs that were conducted in our phase 2 studies are

insufficient for full characterization of impact on liver, but we did do LFTs in our phase 2 studies. And then there is also some literature that we are citing, the Vizeli paper where they gave MDMA to 164 people and did do LFTs pre and post, and Hy's law criteria was not met. But we recognize that we still need to do more, and our plan is, working with the agency, for a postmarketing study to evaluate impact on liver and liver function; but we're still in discussion about what's the appropriate study for that, but definitely plan on doing it as part of our postmarketing commitments if we get approval.

DR. REBO: Thank you.

DR. NARENDRAN: The next question is from Dr. Fiedorowicz.

DR. FIEDOROWICZ: Yes. Hello. Jess Fiedorowicz, University of Ottawa. I have three questions, thank you. The first one is if there's any evaluation for sex or gender differences in efficacy or side effects in the human studies, and particularly interested in the phase 3 pivotal

trials. I'll save the other questions for later so we don't pile them all up.

DR. YAZAR-KLOSINSKI: So just to clarify, your question is both for efficacy and --

DR. FIEDOROWICZ: Yes.

DR. YAZAR-KLOSINSKI: -- adverse effects?

DR. FIEDOROWICZ: Yes. In the materials, I only saw a discussion of sex differences, and I saw no discussion of gender differences and only sex differences from referencing animal studies. I was wondering if there were any analyses looking for sex or gender differences in the results of the phase 3 pivotal trials in humans.

DR. YAZAR-KLOSINSKI: Thank you. We do have an analysis on whether there was an effect of sex in the efficacy results. What we saw was that both males and females still had results that favored MDMA, and as a reminder, the ratio between the sexes was approximately 2 to 1, which is also what we see in the broader PTSD patient population.

In terms of adverse events, I'll have to check with our team to see if we have a slide that

sorts that, and we can get back to you after the break.

DR. FIEDOROWICZ: Thank you for that.

Question two is if there was any evaluation of expectancy of benefit in any of the phase 3 studies.

DR. YAZAR-KLOSINSKI: Yes. We did conduct a blinding survey as a part of the MAPP2 pivotal phase 3 trial, and I'll invite Dr. Connor to speak to the results.

DR. FIEDOROWICZ: The question was specifically about expectancy of benefit, not blinding.

DR. YAZAR-KLOSINSKI: We understand. There was additional information collected in the blinding survey.

DR. FIEDOROWICZ: Okay. Thank you.

DR. CONNOR: Hi. I'm Jason Connor, statistical consultant to Lykos from ConfluenceStat and Assistant Professor of Medical Education at the University of Central Florida College of Medicine. This slide I hope answers the question. So we

asked patients after therapy -- this is from MAPP2 -- which drug they thought they may have received. The high expectancy group are patients who believed they received MDMA; the low expectancy group is patients who didn't know or thought they received placebo.

These are the plots we're used to seeing in the core. The left side shows patients by group who thought they received MDMA, and you can see large effects in both groups, including the 25 percent, approximately, of placebo patients who thought they received MDMA, but large 20-point effects in both groups.

On the right side are patients who did not think they received MDMA; the 75 percent of placebo patients saw attenuated 10-point effects. But even the 3 patients -- and there were minimal; most patients correctly identified that they did receive MDMA. But the 3 patients who did not think they received MDMA, but did, still experienced this 25-point benefit here. The improvements were 18, 21, and 36 points in those 3 patients.

DR. FIEDOROWICZ: So these appear to be assessments of the integrity of the blind. What I'm interested in is what the participants' expectancy of benefit was prior to participating in the study.

DR. CONNOR: I don't think we studied that, but I'd turn --

DR. FIEDOROWICZ: Okay. Thank you.

DR. YAZAR-KLOSINSKI: Unfortunately, we did not collect perspective expectancy.

DR. FIEDOROWICZ: Okay. Thank you for clarifying that.

Then my final question is a follow-up to Elizabeth's question. I was wondering what percent of recruitment came from the website versus clinician referrals, if that data is available; and then if we have any sense, from the website referrals, of how far people were traveling to participate in this study.

DR. YAZAR-KLOSINSKI: We did expect that participants were geographically proximal to the clinical trial sites. These are studies that were

18-week studies, essentially, so it's a lot of visits going back and forth to the clinical trial site, and that was the rationale. In terms of the percentage from the recruitment website versus referrals, that's something we'll have to get back to you. It's not something that we have available at the moment.

DR. FIEDOROWICZ: Understood. Thank you so much.

DR. NARENDRAN: Our next question is from Dr. Canuso.

DR. CANUSO: Hi. Carla Canuso, industry rep. So my question pertains to the MPLONG study and better understanding the durability of effect and interpreting those data. Could you speak to some of the intercurrent therapies that patients received in the duration between the end of the pivotal studies and the follow-up visit, both pharmacological and psychological therapies?

DR. YAZAR-KLOSINSKI: Yes. So in MPLONG, the timing of those studies for the MAPP1 cohort was typically 12 to 24 months after the last

medication session, and in the MAPP2 cohort, it was typically 6 to 12 months after the last medication session, and that was influenced by the fact that the MPLONG study was opened 7 months after the end of the MAPP1 study.

In terms of the types of intercurrent interventions that participants received, this slide summarizes the types of psychotherapy that participants received. And just to draw your attention to the typical trauma-focused psychotherapies that are generally used to target PTSD treatment, those include eye movement desensitization reprocessing, which was 9 percent in the MDMA group and 18 percent in the placebo with therapy group. Also cognitive behavioral therapy, prolonged exposure, and cognitive processing therapy, those are the ones that are typically regarded as the standard of care for PTSD treatment.

DR. CANUSO: What is the other?

DR. YAZAR-KLOSINSKI: The other is essentially open category that captures talk

therapy that doesn't have a specific type of psychotherapy modality assigned to it.

DR. CANUSO: And about pharmacological treatment?

DR. YAZAR-KLOSINSKI: Yes. That's something maybe our team can bring up in terms of the types of pharmacotherapy that was received. I'll have to check with them. Here we go.

Here are the medications that were taken in between the phase 3 parent study and MPLONG, so you can see there was a variety of types of medications. Perhaps antidepressants would be the one that would be of interest given the population, but we also saw that individuals had to take psychostimulants for ADHD, for example.

DR. CANUSO: And any off-label treatments?

DR. YAZAR-KLOSINSKI: We did not collect whether these were on label or off label as a part our data collection.

DR. CANUSO: Thank you.

DR. NARENDRAN: The next question is from Dr. Dunn.

DR. DUNN: Walter Dunn, UCLA and the VA. Three questions, the unblinding questionnaire, those were administered to the subjects. What about the therapists and the independent raters; did you assess whether they knew what the patients were taking? First question.

DR. YAZAR-KLOSINSKI: We did not collect the blinding survey from the therapists or the independent raters.

DR. DUNN: Okay. The second question is regarding the the split dose. You mentioned that the phase 2 trials explored different parameters for treatment. Was it ever looked at to see if a single dose -- not necessarily the total dose, but just a single dose -- was sufficient to catalyze the effective treatment?

DR. YAZAR-KLOSINSKI: There were 9 participants in the very first PTSD clinical trial that received a single dose, and from that point onward, the rest of the program was all based off of a split-dose dosing regimen, so there's not sufficient data to be able to assess whether the

9 participants had sufficient response.

DR. DUNN: And related to that, did you collect any data to see if the intensity of the acute medication experience correlated with outcomes?

DR. YAZAR-KLOSINSKI: We have not been able to conduct that analysis because we did not collect the subjective effects during the acute period; however, in our phase 2 studies, we did collect the subjective units of distress, however, it's not something we've yet analyzed.

DR. DUNN: And the third question is related to the role of the two therapists upon a clinical rollout. There seems to be some discrepancy between the agency's proposed REMS and what you described in your presentation. My understanding is that, previously, there was potentially one license and one unlicensed therapist that was permitted. What's the sponsor's position on clinical rollout? Do both therapists need to be licensed or is one licensed and one unlicensed sufficient?

DR. YAZAR-KLOSINSKI: Dr. Lilienstein?

DR. LILIENSTEIN: Both will be healthcare providers. One is licensed and the other can be on a path to licensure, so making space for people who are in their learning process still, or in development but working towards licensure.

DR. DUNN: And related to that, does the sponsor have any guidance regarding the types of relationships between the two co-therapists? And I'm referring to, again, the misconduct, sexual misconduct, and probably criminal violations that occurred in the phase 2 trial.

My concern is about potential conflicts of interest between the two therapists, especially if they're there to provide safety; and if transgressions are going to occur, that one of the therapists needs to intervene, or step in, or potentially report them to the professional boards. Now, if you've got two therapists that are in either a fiduciary or personal relationship, might there not be a conflict of interest that might prevent them or reduce the likelihood that they'll

intervene?

DR. YAZAR-KLOSINSKI: I'll be able to answer this one. We acknowledge the concern, and it is a valid point. It's something that therapists are also acutely aware of in terms of the importance of limiting conflict of interest as a part of their regulated psychotherapy practice. That's something that we agree is worth considering and putting some guardrails under.

DR. DUNN: So if I understand correctly, right now that's something that you're talking about, thinking about, but that's not something where you might, again, preclude a co-therapy where they're either partners or married; because the incident we're talking about in the phase 2 trials, they were a married couple. And again, I don't know if that factors into whether Dr. Dryer did not intervene or did not report what happened to the regulatory agencies, but you could certainly imagine that -- and my understanding is that many of the co-therapists in your trials were actually in some type of personal relationship, so is that

something you actually might preclude or exclude on clinical rollout?

DR. YAZAR-KLOSINSKI: Yes, that's something we'll take under advisement.

DR. DUNN: Thank you.

DR. NARENDRAN: The next question is from Dr. Iyengar.

DR. IYENGAR: My first question is how did the results for the severe subgroup in MAPP2 compare with the results in MAPP1? And the second question I have is, I understand that the week 18 result is the primary endpoint, but you showed differences at week 7 already. Are those standard error bars taking into account the multiple testing or are they marginal errors?

DR. YAZAR-KLOSINSKI: I'll take this question in two parts. One is, how do we see whether there was an effective baseline severity on the results from the primary model? I don't exactly have the comparison you're speaking of, comparing the severe subgroup from MAPP2 to MAPP1, but we did look at whether baseline severity had an

effect in terms of the moderate group, which came entirely from MAPP2 versus severe in a pooled analysis. This forest plot shows that both moderate and severe PTSD patients responded similarly, and baseline severity did not seem to have an effect in the pooled sample.

In terms of the analyses for the standard efficacy, I'll invite Dr. Connor to speak to that.

DR. CONNOR: Jason Connor, statistical consultant to Lykos. Because the prespecified primary analysis was the week 18, and we didn't have, for example, alpha spending to the previous weeks, what you see are the nominal error bars and non-multiplicity adjusted.

DR. IYENGAR: Thank you.

DR. NARENDRAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Were CAP scores collected after the first round, second round? I know they were at the end of the third, but I'm curious if there's any data through the process. That's my first question, and we'll start there.

DR. YAZAR-KLOSINSKI: Sure. I'll bring up the slide from the core presentation, which I think will facilitate the answer. The purple triangle is the independent rater visit for the CAPS-5 and the Sheehan Disability Scale; so yes, it was collected in between the second and third integration psychotherapy visits and treatment cycles 1 and 2, and then the treatment cycle 3 effect was measured at the primary endpoint. So the results over time, here's MAPP1 and MAPP2, so those interim purple triangles, they correspond to week 7 and week 12, which are shown here.

DR. JONIAK-GRANT: Thank you for that.

Then my other question concerns the lack of diversity in the studies. Recently, in Frontiers in Psychiatry, there was some discussion that MDMA had shown improved health outcomes for white users, but at times minimal if any improvement for other racial or ethnic groups. There can also be significant variation in benefits depending on education, income, et cetera; and yet the clinical trial participants were largely white. I think it

was 85 and 70 percent white for all of phase 3. There were 5 black participants and I believe 7 Asian in the MDMA arm of things. So I just wanted to give you-all an opportunity to maybe talk about that and address that issue.

DR. YAZAR-KLOSINSKI: We acknowledge that this is a bit of a challenge in terms of our program. What we did do is examine whether there was any treatment response differences among white versus non-white participants, and we saw that although the confidence interval does cover zero a little bit on the non-white, the group still favored MDMA; both groups still favored MDMA.

In terms of the exposure levels, we did receive data from the National Institute of Drug Abuse that had 73 percent African American participants. So from a exposure standpoint, there were no differences; the race covariate was not significant. We also implemented a diversity plan during the first phase 3 study; however, the benefits of that diversity plan were only able to be realized for the second phase 3 study, so we are

committed to improving on this and continuing to examine this question as we have larger numbers. As PTSD is a serious condition, the clinical trials are giving us a read on what the benefit might look like, and we'll continue to study that post-approval.

DR. JONIAK-GRANT: Thank you for that. And do you have similar data for adverse events, where it's divided up for white and non-white?

DR. YAZAR-KLOSINSKI: I'll have to check --

DR. JONIAK-GRANT: Okay.

DR. YAZAR-KLOSINSKI: -- with our team about that at the break.

DR. JONIAK-GRANT: Thank you.

DR. NARENDRAN: The next question is from Dr. Barone, who's virtual.

DR. BARONE: Hi. Melissa Barone, the Maryland Health Care System. Regarding treatment response outcomes, for participants who were rated as 47 or higher on the CAPS-5 total score, which would be like in the extreme range, were there any differences between them and the groups that were

rated as severe or moderate?

DR. YAZAR-KLOSINSKI: There were very few participants who were in the extreme range on the CAPS-5, so the small number precludes our ability to identify any trends.

DR. BARONE: Thank you.

DR. NARENDRAN: This is Raj Narendran. I had a couple of questions. Looking at your inclusion/exclusion criteria, do you still plan to exclude people with borderline personality disorder who typically have a lot of childhood trauma, complex PTSD? One could argue they are probably all PTSD. So would you exclude them? Would you also continue to propose to exclude people with substance use like cocaine, or methamphetamine, or anyone who used psychostimulants?

DR. YAZAR-KLOSINSKI: In terms of our plans for the label, I'll invite Dr. Lilienstein to speak to that.

DR. LILIENSTEIN: Dr. Lilienstein, Lykos Therapeutics. These are populations, as you clearly state, that have not been studied, so we

don't have data to report from the phase 3 clinical trials for substance-use disorder other than alcohol and cannabis. Our proposed label would indicate that these haven't been studied and that it would be a benefit-risk conversation between the provider and the patient to determine whether the potential benefits might outweigh the risks for those individual patients and what they may be.

I recognize the two populations you mentioned have different risks, potentially, and I think the prescriber and the therapist would need to work together to determine what might be the safe way to move forward if the benefits do outweigh the risks.

DR. NARENDRAN: Another question while I have you there, the tachycardia issue and hypertension, this is relatively high dose, your MDMA. I've given a lot of amphetamine to subjects, dextroamphetamine for research studies, and we do see a lot of tachycardia.

Are there clear cutoffs to intervene? Would the label have don't discharge them if it's over

120? And you didn't collect any EKGs after the medication to really provide clear guidance on -- there could be other arrhythmias happening. You could have ventricular tachycardia; you could have had other kinds of sinus arrhythmias; you could have had blocks; you could have had things that you don't know.

So what would be the guidance for people on the label when they discharge them?

DR. LILIENSTEIN: I'm going to invite my colleague, Dr. Kowey, to come speak to that.

DR. KOWEY: Peter Kowey. I'm a cardiologist and electrophysiologist in Philadelphia, Lankenau Heart Institute and Jefferson, and I'm here -- as you've heard, paid my time and travel.

It's obviously a very important question because safeguarding patients during this relatively short period of time at which they're at risk is critically important, so a number of thoughts about that. First, as you recall, the patient selection here was very, very careful. Patients were at low risk, and if they weren't at

very low risk, they were screened with exercise testing and suitable other tests, cardiac tests, so obviously, patients that went into this study were highly selected, and they should be, as the program rolls out, until we have more experience with this.

Second is that we actually have data provoking arrhythmias in people who do not have heart disease using catecholamines, for example. It's extremely unusual for patients to have a clinically significant arrhythmia such as VT, ventricular tachycardia, or super ventricular tachycardia, in the absence of symptoms, and as you recall from the clinical trial, there weren't any patients who had a cardiac rhythm SAE or AE.

So although we cannot tell you incontrovertibly that that could not have happened, I think the likelihood is very low. And the reason why I think that's important is because attempting to monitor patients during the course of this clinical experience that they're having with their therapist would clearly interfere with the therapeutic relationship. So based on the empiric

data that have been accumulated and what we know about this kind of a situation, I think, for the time being at least, I wouldn't recommend that there be online monitoring.

DR. NARENDRAN: I think we're almost out of time, so I think we'll probably take a quick 10-minute break.

Panel members, please remember that there should be no chatting or discussion with the meeting topics during break. We will resume at 11:10. We will resume at 11:10.

(Whereupon, at 10:57 a.m., a recess was taken, and meeting resumed at 11:11 a.m.)

DR. NARENDRAN: We will now proceed with the FDA's presentations, starting with Dr. David Millis.

FDA Presentation - David Millis

DR. MILLIS: Good morning, everyone. My name is David Millis. I am the primary clinical reviewer for this application within the Division of Psychiatry at FDA. Today, together with Dr. Olivia Morgan, from the Division of

Biometrics I, I will be presenting the division's assessment to date of the new drug application for midomafetamine capsules.

I will start by providing a brief introduction, focusing on both midomafetamine itself and the indication being sought, which is the treatment of posttraumatic stress disorder or PTSD. From there, I will give an overview of the relevant regulatory history, highlighting some key discussions and how they relate to the review issues we will be presenting today.

Dr. Morgan will present the efficacy analyses, then turn the presentation back to me for a discussion of safety issues. From there, I will turn the presentation over to Dr. Victoria Sammarco from the Division of Risk Management to describe the agency's current thinking on the need for our risk evaluation and mitigation strategy, or REMS, if this product were to be approved, and some details about what a REMS might look like here. Following the presentations, there will be time for the committee to ask clarifying questions.

First, I'll begin with some information about PTSD and midomafetamine. Post-traumatic stress disorder is a severe and debilitating psychiatric condition that can affect anyone following exposure to actual or threatened death, serious injury, or violence, including sexual assault. PTSD is characterized by symptoms such as intrusive memories or flashbacks; nightmares; hyperarousal; and avoidant behavior. These symptoms can seriously impair daily functioning and relationships.

The condition is highly comorbid with other major psychiatric disorders, and individuals with PTSD have a high risk of suicidal ideation and behavior, mood and anxiety disorders, and substance-use disorders. The overall prevalence of PTSD is fairly high, with around 5 percent of the U.S. population having PTSD in any given year and an estimated prevalence of around 13 million Americans living with PTSD.

Today, we are here to discuss our review of midomafetamine for the treatment of PTSD in adults.

Midomafetamine has a similar chemical structure to the amphetamine class of drugs. Pharmacologically, it acts as a serotonin, norepinephrine, and dopamine reuptake inhibitor and releasing agent. For the proposed treatment paradigm, the drug is taken orally with three supervised dosing sessions that are at least 3 weeks apart over a total course of 4 months.

The applicant has proposed that midomafetamine be administered in combination with a program of psychological intervention. In the clinical trials, the psychological intervention consisted of preparatory sessions separate from and prior to medication administration, psychological support during medication administration sessions, and regularly scheduled integrative psychotherapeutic sessions between medication sessions. This treatment is proposed to be administered in an outpatient setting with supervision by appropriate personnel for 8 hours or more until the acute effects of midomafetamine resolve.

Even though PTSD is a common disorder, we have very few medications approved for this indication. Only paroxetine and sertraline -- both selective serotonin reuptake inhibitors, or SSRIs -- are approved for the treatment of PTSD, with the most recent of these approvals more than two decades ago in 2000. The response rate for these medications rarely exceeds 60 percent, with less than 20 to 30 percent of patients achieving symptom remission. It can take up to 12 weeks to experience a treatment effect, and these medications are intended for chronic daily administration.

SSRIs are generally well tolerated, but they can cause gastrointestinal adverse reactions and sexual dysfunction, and they have a boxed warning for suicidal ideation and behavior in pediatric patients and young adults. Off-label treatment for PTSD is common, with a number and range of off-label treatment options, possibly a reflection of the limitations of the approved treatments.

Several treatment guidelines recommend

certain modalities of psychotherapy, either alone or in combination with pharmacotherapy, as first-line treatment for PTSD. Therapies with empiric support include cognitive behavioral therapy, both general and trauma focused, and eye movement desensitization and reprocessing, or EMDR, among others.

The applicant is proposing a novel treatment paradigm. Rather than chronic daily administration, the proposed midomafetamine regimen is more circumscribed. It is administered in three separate dosing sessions. Each dosage is split into an initial larger dose, followed 1.2 to 2 hours later by a second smaller dose, with this separation intended to improve tolerability.

Just to clarify, the doses on this slide are the doses of the freebase molecule rather than the hydrochloride salt, so the doses will look a little different from the doses that you saw in the applicant's slide, but these are how the doses would appear in the product labeling if the product is approved. The total dosage in the first session

is 102 milligrams. The total in the two subsequent sessions is 150 milligrams. There are at least 3 weeks between each dosing session. This time-limited treatment is intended to provide lasting relief from PTSD symptoms.

I will now provide the regulatory history of this development program, highlighting some key discussions between FDA and the applicant. Because this is a complex development program with more than 20 years of regulatory history, I'm going to present the history by issue rather than with a simple chronology.

I will start with our discussions with the applicant related to functional unblinding. The investigational new drug application, or IND, for midomafetamine was opened in 2001 with a proposal for a double-blind, 20-patient study in individuals with PTSD. Over the next several years, the applicant conducted a number of small phase 1 and phase 2 studies.

In 2016, the applicant met with FDA for an end-of-phase 2 meeting. End-of-phase 2 meetings

are considered milestone meetings in drug development. Discussions typically involve a presentation of top-line safety and efficacy data from early-phase studies and a proposal for the design of phase 3 studies intended to establish the safety and efficacy of the product.

At the end-of-phase 2 meeting for this program, a major concern was how to address the potential for functional unblinding given that the drug's effects are readily perceived by people taking the drug compared to placebo, which could lead to expectation bias. FDA suggested that the applicant could include an active comparator arm rather than a placebo to mitigate the impact of unblinding and expectation bias. The applicant identified concerns with each comparator suggested, and the matter remained unresolved at the conclusion of that meeting.

Why are we so concerned about functional unblinding? Well, we rely on data from adequate and well-controlled trials to provide the basis for substantial evidence of effectiveness. Among other

characteristics, to be considered adequate and well controlled, a study must incorporate a design that permits valid comparison with a controlled condition and measures must be taken to minimize bias. Randomized, double-blind, placebo-controlled trials are the usual gold standard for adequate and well-controlled trials.

If a study is unblinded, the results may become unduly influenced by expectation bias. Both participants and the investigators working with them may behave or think differently if they are aware of the treatment assignment. They may be relieved that the treatment will work if they know that the subject has been assigned to the treatment arm and conversely may express or feel disappointed if they know that the participant is receiving placebo instead.

These effects can lead to inflated reports of benefit in the treatment arm and, conversely, to flat or worsening symptoms ratings in the placebo arm. Study dropouts also may increase in the placebo arm, which can affect statistical analyses.

Bias may also affect investigators' assessments of a participant's symptoms, either consciously or unconsciously. Ultimately, functional unblinding complicates the interpretation of trial data. Any evaluation of treatment effects needs to take into consideration the influence that known and unknown biases could have had on the study results.

In January 2017, the applicant submitted their first phase 3 study protocol called MAPP1. Recognizing that this would be a challenging program, the applicant asked for agreement in advance that the protocol design would be appropriate for a study designed to support a marketing application. The process by which they requested this agreement is known as a special protocol assessment or SPA. We did not agree to the SPA as initially submitted. We had concerns about the applicant's proposed statistical analyses and choice of secondary endpoint, but we did find some elements of the protocol acceptable. For instance, the applicant outlined a plan to minimize bias by using blinded centralized independent

raters to administer the primary outcome measure via video interviews.

We did agree to the use of midomafetamine-assisted psychotherapy as the treatment arm and identical psychotherapy with inactive placebo as a controlled condition, but expressed continued concern about the adequacy of blinding. We also agreed to the applicant's proposed definitions of treatment response, loss of diagnosis, and remission based on the clinician-administered PTSD scale for DSM-5 or CAPS-5 score change.

The agency provided extensive feedback to the applicant's plans for monitoring cardiac safety and for collecting abuse-related address events, which we will address in more detail later in our presentation.

In May 2017, we met with the applicant to discuss the no agreement letter and to provide advice on a resubmission. At that meeting, the agency noted that the second phase 3 study, MAPP2, would not require a separate SPA given that it

would have essentially the same design as MAPP1. The agency also agreed that no new animal or human abuse potential studies would be required given this drug's known abuse potential.

In July 2017, we reached agreement on the revised SPA. In doing so, the agency agreed that the design and planned analysis of the proposed study is adequate to address objectives necessary to support a regulatory submission; however, agreement on an SPA does not guarantee that the trial results will be deemed adequate to support approval. This decision can only be addressed during review of the submitted NDA and is based on the adequacy of the overall submission.

I will now discuss the agency's advice to the applicant regarding the assessment of adverse events related to abuse potential in their phase 3 studies. In the March 2017 SPA no agreement letter discussed earlier, we communicated to the applicant that adverse events related to a potential abuse or overdose concerns in all the studies need to be documented, and referred the applicant to our 2017

guidance, "Assessment of Abuse Potential of Drugs," for details about these expectations. Here, I've highlighted some of the specific recommendations from the guidance for documenting effects on the central nervous system like euphoria and other events that may indicate drug liking or abuse potential.

However, in reviewing the clinical study reports submitted with the application, we noticed the striking lack of abuse-related adverse events. When we followed up with the applicant about their abuse potential assessment methodology, they clarified that they did not systematically collect abuse-related adverse events as advised in the guidance; rather, they only documented events characterized as unfavorable.

This lack of systematic collection of positive events is a major concern because this is key data that would help us characterize the central nervous system effects of the drug. As a result of not having this data, our ability to properly describe the expected frequency and

severity of these events in product labeling is affected. For instance, although we may be able to include a general description and warnings and precautions of known effects of midomafetamine based on literature, we have no verbatim adverse event terms, so no descriptions of the midomafetamine experience in participants' own words.

This information could have helped us to determine the best language to describe these effects in the prescribing information. Further, there is no data to quantify the frequency of euphoria or other abuse-related events in the adverse reaction section of the labeling.

We also don't know when participants began to feel the effects of midomafetamine, nor when those effects resolved. This data could help inform recommendations related to appropriate monitoring duration and assessment of discharge readiness after medication sessions.

Returning to the regulatory history, there are a few more events of note. In 2017, the

applicant applied for and was granted Breakthrough Therapy Designation based on past results of their phase 1 and phase 2 studies. After reviewing an amendment to the MAPP2 protocol, we asked the applicant to include a participant blinding survey in the study to help better characterize the influence of unblinding. The applicant agreed to do so, and during the May 2023 pre-NDA meeting agreed to submit the results with their NDA.

Finally, during our last few meetings with the applicant, we noticed some additional review concerns. During a breakthrough therapy advice meeting in September 2022, we noted that the safety database for the development program would be considered inadequate if the drug required chronic or chronic intermittent administration to maintain a treatment effect. This question of durability is relevant here; because PTSD is a chronic condition, any proposed treatment for PTSD should take this factor into account.

The applicant proposed to address this question by providing the results of their

exploratory follow-up observational study, MPLONG, which consisted of a single follow-up assessment of participants from MAPP1 and MAPP2 at least 6 months after the last dosing session. During the meeting with the applicant, we noted that MPLONG was likely inadequate to fully address the question of durability of effect, but the agency would review the results with an NDA submission.

At the pre-NDA meeting, the agency noted that a risk evaluation and mitigation strategy, or REMS, would likely be required if this drug were to be approved, but that the specific risk to be mitigated by any proposed REMS would be a matter of review. A REMS is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh the risks. Dr. Sammarco will provide details about the agency's proposed REMS during her presentation.

The last major review issue we want to highlight here is the role of the psychological intervention in this development program. As

previously noted, during the March 2017 SPA discussion, the applicant asked about the acceptability of their proposed plan to include psychotherapy in both drug and placebo arms in their phase 3 studies. The agency noted ongoing concerns about unblinding and results and bias, but ultimately agreed with their study design.

During the rest of the development program, neither the applicant nor the agency inquired or discussed any further details regarding how the psychotherapy program might be described in labeling; however, FDA does not regulate psychotherapy, and our ability to describe concomitant psychotherapy or behavioral interventions in labeling is limited.

The goal of the psychological intervention in the clinical trials varied at different stages of treatment. Starting with the three preparatory sessions prior to the medication session, the goal of these sessions was to orient and provide psychoeducation regarding what to expect with treatment before dosing began. The three

medication sessions lasted at least 8 hours apiece. The psychological intervention during the medication session consisted of general psychological support, as well as observation for safety purposes. Direct therapy was minimal. After each dosing session, there were three integrated sessions for a total of nine integrative sessions over the course of the study.

The purpose of the integrative sessions was to help the participants describe their experience of the medication sessions, particularly the experience of remembering trauma. These were the main sessions where the more primary psychotherapeutic interaction occurred; however, the content or approach of these integrated sessions was not standardized in the treatment manuals and was mainly left up to the individual therapist. The manual provided general guidelines orienting the therapist to an appropriate therapeutic stance towards the participants and setting, but not being directive or specific in terms of the content or approach of those therapy

sessions. The approach to therapy was not standardized and could vary considerably from therapist to therapist.

Overall, we note that it's difficult then to assess how the psychological intervention provided by the applicant in the studies contributed to the overall treatment effect and results. The study design did not allow for any comparisons between drug alone, versus therapy alone, versus the paired treatment, or for any comparisons with other therapeutic modalities compared to the applicant's manualized therapy; and as noted already, we do not regulate therapy as a rule in terms of its specific content or details.

Labeling regulations allow for specification that a drug should be used only in conjunction with another mode of therapy, but that generally requires evidence that the other mode of therapy is necessary to achieve a treatment effect. Under a REMS, we could require monitoring to ensure a patient's safety, but a REMS cannot dictate that a patient is offered or engages in psychotherapy.

I will now provide an overview of the phase 3 studies submitted for our review with this NDA. MAPP1 and MAPP2 were both randomized, double-blind, placebo-controlled studies comparing the use of midomafetamine plus psychological intervention to placebo plus psychological intervention in the treatment of PTSD. The primary difference between the two studies was severity of participant symptoms. MAPP1 enrolled participants with severe PTSD, whereas MAPP2 enrolled participants with moderate or severe PTSD.

MPLONG was an observational follow-up study that consisted of a single follow-up assessment at least 6 months after participants completed either MAPP1 or MAPP2. This assessment was intended to explore durability of treatment effect.

The applicant has already presented the details of the study designs and demographics of their populations; however, I do want to spend some time discussing the primary endpoint for the phase 3 studies, which is a mean change from baseline on the CAPS-5 at week 18.

The CAPS-5 is a 30-item clinician-reported outcome measure. In the phase 3 studies, a blinded centralized independent clinician rater conducted a semi-structured interview to assess key symptoms of PTSD over the previous month. Versions of the CAPS have been the most commonly used assessment measure for PTSD for decades. The CAPS-5 reflects recent adaptations to align with the DSM-5 criteria.

Each item on the CAPS-5 is rated from 0 to 4 for severity. A total severity score is generated by summing the individual scores for the first 20 items of the scale, with a total highest score possible of 80. The scale was administered 4 times for each participant in the phase 3 studies at baseline, then approximately at week 6, 12, and at the prespecified primary endpoint at week 18. However, there was some variability in the timepoints for each participant, especially the exploratory intermediate endpoints at approximately week 6 and week 12.

Here we list the symptoms covered by each of the first 20 items on the CAPS-5. As you can see,

the list of symptoms assessed by the CAPS-5 aligns directly with the diagnostic criteria in the DSM-5. During discussions with the applicant and in consultation with our internal clinical outcome assessment experts, we agreed that a 10-point or greater change on the CAPS-5 score reflected a treatment response. Our literature review examining how individual items on the scale contributed to the overall total score indicated that 10 points appears to be in the range of clinically meaningful within patient change.

With that overview in mind, I now want to turn the presentation over to Dr. Olivia Morgan to present the efficacy data from the clinical studies.

FDA Presentation - Olivia Morgan

DR. MORGAN: Thank you, Dr. Millis.

The primary endpoint for MAPP1 and MAPP2, the change from baseline in CAPS-5 total severity score to 18 weeks after baseline, was analyzed using a mixed model for repeated measures or MMRM. In this slide, we've presented the estimated mean

change from baseline to week 18 in CAPS-5 total severity score for both studies. The results for MAPP1 are on the left side of the table and the results from MAPP2 are on the right side of the table. The difference between the midomafetamine arm and placebo arm is shown in the bottom half of the table.

In both studies, there was a statistically significant difference between the midomafetamine arm and placebo arm in reduction in CAPS-5 scores at week 18. In MAPP1, there was an estimated 11.86-point larger reduction in LS mean change from baseline in CAPS-5 scores for participants randomized to midomafetamine compared to those randomized to placebo. In MAPP2, there was an estimated 8.91-point greater reduction in LS mean change from baseline for participants in the midomafetamine arm compared to those in the placebo arm.

In MAPP1 and MAPP2, around 12 percent and 8 percent of the participants, respectively, had missing efficacy outcomes at week 18. To explore

the impact of missing data on the primary analysis results, a sensitivity analysis, which is based on the tipping point analysis, was conducted. The sensitivity analysis suggested the results of the primary analysis were robust to deviations from the missing-at-random assumption; however, the functional unblinding of the studies may have had some impact on the observed results.

As mentioned earlier, the agency agreed to a 10-point or greater change on the CAPS-5 score as the threshold for a treatment response during the development program. In both MAPP1 and MAPP2, the LS mean change from baseline to week 18 in CAPS-5 score was larger than 10 points in both the midomafetamine and placebo arm, so the mean change in both groups can be considered clinically meaningful; however, participants in the midomafetamine arms experienced a mean change from baseline of around 24 points in contrast to participants in the placebo groups who had about a 13 to 14 point change in CAPS-5 scores. The change from baseline for participants in the

midomafetamine arm was around 9 to 12 points larger than in the placebo arm.

To control the overall type 1 error rate, the applicant used a hierarchical testing strategy. If the analysis of the primary endpoint was statistically significant, the applicant tested the key secondary endpoint, the Sheehan Disability Scale, or SDS, total score. The SDS is a 3-item scale with each item rated on a scale of 0 to 10 for a total possible score range of 0 to 30. Higher scores indicated greater disability or functional impairment. The key secondary endpoint, the change from baseline in SDS total score to week 18 after baseline, was analyzed using a similar MMRM model as the one used for the primary endpoint.

In this table, we've presented the estimated LS mean change from baseline to week 18 in the SDS total score for both studies. The results for MAPP1 are on the left side and the results for MAPP2 are on the right. Results of both studies showed a statistically significant difference

between the midomafetamine arm and the placebo arm in reduction in SDS scores. In MAPP1, participants in the midomafetamine arm had an estimated 1.36-point larger decrease in the LS mean change in SDS scores from baseline compared to those in the placebo arm. In MAPP2, participants in the midomafetamine arm had a 1.2-point larger decrease in the LS mean change in SDS scores from baseline compared to the placebo arm.

At the agency's request, the applicant incorporated an unblinding survey into the protocol for MAPP2 to assess the degree to which participants could correctly guess their treatment arm assignment. The results are shown on this slide. Among participants in the midomafetamine arm, 79 percent reported they were positive they received active drug and 15 percent reported they thought they received active drug. Among participants in the placebo arm, 43 percent were positive they received placebo and 32 percent thought they received placebo.

The results of the unblinding survey from

MAPP2 indicate that study participants could guess their treatment arm assignment with a high degree of accuracy. Additionally, a higher proportion of participants in the active drug arm compared to those in the placebo arm correctly guessed their treatment assignment. This was likely also true for participants from MAPP1, but an unblinding survey was not requested or conducted for that study.

There is no straightforward way to account for the impact of functional unblinding on the estimated efficacy results for MAPP1, MAPP2, or the long-term follow-up study, MPLONG. This is a limitation of these studies, and the results should be interpreted with this in mind.

I will now move on to presenting the results of the efficacy analysis for the long-term follow-up study, MPLONG. MPLONG enrolled participants from the parent studies MAPP1 and MAPP2 for a single visit at least 6 months after the end of the parent studies; however, not everyone from the parent studies enrolled in

MPLONG. The percent of treated participants from MAPP1 and MAPP2 who enrolled in MPLONG and the percent who completed a CAPS-5 assessment in MPLONG are shown in this slide. Sixty-two percent of treated participants from MAPP1 and 78 percent of treated participants in MAPP2 completed a CAPS-5 assessment in MPLONG.

The mean CAPS-5 score at MAPP1 and MAPP2 study termination is shown in this table. The columns represent treatment arm and the rows represent whether or not participants enrolled in MPLONG. Participants who enrolled in MPLONG, as shown in the top row, had a lower mean CAPS-5 score at parent study termination compared to those who chose not to enroll, as shown in the bottom row. So on average, participants who did not enroll in MPLONG had more PTSD symptoms at the end of the parent studies as measured by the CAPS-5 score.

The change from MAPP1 or MAPP2 baseline in CAPS-5 total severity score was analyzed using an MMRM, the same as the analysis of the CAPS-5 score conducted in the parent studies. Note that there

is no plan to control the type 1 error rate in the study, and the results are considered strictly exploratory. We presented the results for participants from MAPP1 and MAPP2 separately because participants from MAPP1 were unblinded prior to enrolling in MPLONG.

For participants from MAPP2 and in the midomafetamine arm, at week 18, there was an estimated 24.4-point decrease in LS mean change from baseline in CAPS-5 score. At the long-term follow-up visit 1, there was an estimated 28-point decrease from baseline. Comparing between the two visits, there was an additional 3.6-point decrease at the long-term follow-up visit. For participants for MAPP2 and in the placebo arm, there was essentially no difference between week 18 and the long-term follow-up visit 1 in LS mean change from baseline in CAPS-5 scores.

One limitation of the study is the variable timing of the long-term follow-up visit 1. The visit occurred at least 6 months but up to 2 years after the last dose in the parent study. MAPP1 was

conducted before MAPP2, and there was a longer lag time between MAPP1 and MPLONG, so the long-term follow-up assessment was generally later for those participants. Another limitation of MPLONG is that some participants reported using non-study drug interventions in the interim period between the parent study and MPLONG. Participants from MAPP1 and MAPP2 reported using ketamine; the psychedelic, 5-MEO-DMT; or illicit MDMA.

The number of participants entering MPLONG from MAPP1 and MAPP2, who reported use of these psychoactive substances in the interim period between parent study and MPLONG, is shown in this table. There were 17 participants in the drug arm and 13 participants in the placebo arm who reported the use of at least one of these psychoactive substances. It is also possible that there may be additional unreported non-study drug use in the interim period.

To assess the potential impact of the interim use of other psychotropic substances, the agency conducted a few exploratory analyses, all by

treating any data collected after interim use as missing. In one, we repeated the efficacy analysis for MPLONG on the effectiveness subset; in another, we included everyone in the mITT population for MAPP1 and MAPP2 and imputed all missing data under the missing-at-random assumption using a multiple imputation technique. The missing-at-random assumption is the same assumption imposed in efficacy analyses. Generally speaking, it implies that the response trajectories of participants with missing data were similar, on average, to those with observed data in the same treatment group.

Based on our exploratory analyses, the use of ketamine, 5-MEO-DMT, or illicit MDMA in the interim period may have had some impact on the estimate at the long-term follow-up visit, but that impact is difficult to quantify.

The results of the analyses I just described are presented here. The top row includes the estimated change from week 18 to the long-term follow-up visit 1 in LS mean change from baseline for all observed CAPS-5 scores, which are the

results I've already presented. The second row presents the estimated change from week 18 when data collected after interim use was treated as missing and the efficacy subset was used. The bottom row represents the estimated change from week 18 when data collected after interim use was treated as missing. The full mITT set from both parent studies was used and all missing data was imputed under the missing-at-random assumption.

The impact of removing data collected after interim use and of imputing missing values varies by parent study and arm. For example, for participants from MAPP2, if we remove data collected after interim use, the results got worse in the midomafetamine arm but got better in the placebo arm; however, for participants from MAPP1, the results in the placebo arm were generally stable, but for the midomafetamine arm, it depends on how the data were analyzed.

Keep in mind that MAPP1 was unblinded before participants enrolled in MPLONG, although we cannot rule out impact of functional unblinding for MAPP2.

In addition, for MAPP1, the follow-up duration was generally much longer than in MAPP2 and could have been up to 2 years. Regardless, these findings suggest that there may have been some impact on the interim use on the results of the efficacy analyses from MPLONG.

At this point, I will pass it back to Dr. Millis to summarize the uncertainties about the efficacy data, then continue with the description of safety.

FDA Presentation - David Millis

DR. MILLIS: Thank you, Dr. Morgan.

Listed here are some of the key uncertainties about the efficacy data in these trials. Although we do have two positive studies, these results are in the context of dramatic functional unblinding. We know that it is difficult to control the impact of functional unblinding in psychedelic clinical trials, and the applicant did use blinded central raters to attempt to mitigate the impact of unblinding. Nonetheless, based on the results of the unblinding

questionnaire in MAPP2, it is clear that participants were aware of their treatment assignment, and that could impact their report of symptom control.

As Dr. Farchione noted in her opening comments, a study that is functionally unblinded may still be able to be considered as an adequate and well-controlled study; however, the potential influence of bias needs to be factored into the interpretation of the study results. It is important to consider if there were adequate methods to minimize bias, the magnitude of the treatment effects, the robustness of the study results, and what is known about the natural history of the condition.

We also have some exploratory data suggesting that the effects of midomafetamine may be durable, but this is based on a single follow-up assessment with a high degree of variability and time to visit. Further, because the applicants who enrolled in MPLONG had fared better in the parent study than those who did not enroll, we have

concerns about selection bias. There also remains an unresolved question of the impact of non-study drug use between the parent studies and MPLONG.

Finally, the applicant has presented midomafetamine as an aid to psychotherapy; however, the role of psychotherapy and its contribution to the observed treatment response has not been formally evaluated. Also, given the inherent flexibility in the therapy manual, there may have been considerable variability in therapeutic approach; however, there were no evaluations comparing whether these changes in therapeutic approach had any influence on efficacy.

I will now move on to a review of safety. The most common adverse events detected in the phase 3 trials are listed here with most being consistent with prior published literature on MDMA and the effects of stimulant class and serotonergic drugs. Most adverse events occurred during the medication session and resolved prior to the scheduled discharge at 8 hours. However, as previously noted, we have no information on the

frequency or time course of any abuse-related adverse events if those events were considered positive, favorable, or neutral.

In both MAPP1 and MAPP2, blood pressure and heart rate were assessed at baseline, 1.5 hours after the first dose of study drug and at the end of the medication session. Both blood pressure and heart rate were elevated at the 1.5-hour assessment in the midomafetamine group, with blood pressure returning to baseline by the end of the 8-hour medication session, but heart rate remaining slightly elevated.

Roughly 6 percent of participants in the midomafetamine group experienced elevations in systolic blood pressure exceeding 180 milligrams of mercury compared to no participants in the placebo group. Although no major adverse cardiac events were observed in the development program, rapid elevations in blood pressure and heart rate can increase the risk of myocardial infarction, myocardial ischemia, central nervous system hemorrhage, or aortic dissection. Because the risk

for these events is highest for individuals with pre-existing cardiovascular disease, it will be important to appropriately label these risks if midomafetamine is approved.

We also have concerns about the potential proarrhythmic effects of midomafetamine. A thorough QT study was not performed as part of this development program; however, it is likely that such a study would have been confounded by any drug-related increase in heart rate. The applicant did conduct alternative analyses to evaluate the potential of midomafetamine to prolong the QT interval; however, these analyses covered only about half of a therapeutic dose and the hERG assay did not assess metabolites or include appropriate positive controls. The applicant did submit nonclinical cardiovascular studies, adverse event reports from phase 2 and phase 3 studies, and results of their literature search, suggesting low proarrhythmic potential for midomafetamine.

As part of our review, we consulted the Division of Cardiology and Neurology, who

identified literature cases of arrhythmia associated with illicit MDMA use that were not included in the applicant's literature review; however, these case reports were confounded by other substances and lack data on dose and frequency of use.

In the development program, there was a single serious adverse event of cardiac arrhythmia in one phase 2 study. That participant required emergency room assessment and overnight monitoring. Because that participant had a single premature ventricular contraction on baseline ECG at time of entry into the study, the investigator assessed the participant's repeated ventricular extrasystoles as an exacerbation of pre-existing ventricular ectopy and as likely related to midomafetamine.

Overall, the available data is insufficient to fully assess the cardiovascular risks of midomafetamine; however, the known and potential risks can be described in labeling. In addition, we are considering alternatives for further assessing any QT prolongation potential of

midomafetamine such as a dedicated ECG pharmacodynamic study. Such a study could be performed in the postmarketing setting if this drug is approved.

I will now consider the issue of suicidal ideation and behavior. For all psychiatric drug development programs, the Division of Psychiatry advises that all clinical protocols, regardless of the indication, include a prospective assessment for suicidal ideation and behavior. We are cognizant of the background risk for suicidal ideation and behavior in the study population and are concerned about the potential for a study drug to impact this risk, whether via direct effects from the drug, from the drug leaving one's system, or from the influence or presence of study systemic support.

In this development program, suicidal ideation and behavior was assessed using the Columbia Suicide Severity Rating Scale, which is the most commonly used instrument for assessing and monitoring suicidal ideation and behavior in

clinical trials. Serious adverse events related to suicidal ideation and behavior were minimal and only occurred in the placebo arm for phase 3.

The background rate of suicidal ideation was similar in both treatment arms and comparable to other psychiatric drug development programs. Participants without prior suicidal behavior did not experience an increase or onset of such behavior in the phase 3 studies. The proportion of participants whose suicidal ideation and behavior increased in the study based on C-SSRS rating was similar between drug and placebo arms. Finally, there were no evident patterns of increased suicidal ideation or behavior in the 24 to 72 hour period immediately following the medication sessions.

With regard to other psychiatric adverse events, the adverse events that occurred at higher frequencies in the midomafetamine arm relative to placebo are listed here. Many of these are symptoms consistent with PTSD itself or could be related to stimulant or serotonergic properties of

midomafetamine.

To provide some additional context, this slide lists the psychiatric adverse events occurring in at least 5 percent of midomafetamine-treated participants and greater than placebo in the safety population of the pooled MAPP1 and MAPP2 trials. Insomnia, restlessness, and nervousness could potentially be related to the stimulant properties of midomafetamine. Nightmares, depression, intrusive thoughts, and flashbacks could potentially be related to the underlying PTSD. It may be difficult to draw definitive conclusions about whether these adverse events are drug effects or symptoms of the underlying illness; however, their frequency of occurrence compared to placebo will be included in the product labeling if the drug is approved.

The literature for MDMA describes thermoregulatory and osmoregulatory phenomena are particularly in the context of illicit use in settings like all-night, crowded, overheated rave parties. In the controlled and time-limited

context of the midomafetamine drug development program, thermoregulatory and osmoregulatory adverse events still did occur more commonly in the midomafetamine group than on placebo, but were not associated with any serious events. Our ability to fully characterize these risks is limited by the lack of clinical laboratory data from the phase 3 studies.

Although hepatotoxicity was not treated as an adverse event of special interest during the clinical trials, the applicant included with their NDA submission a report discussing hepatotoxicity as a possible adverse event of special interest based on prior case reports of severe liver injury with illicit MDMA use. There were no adverse events detected in the development program related to liver injury, but there were also no post-baseline liver function laboratory assessments during the phase 3 studies.

Liver function labs were only collected in one phase 1 and two phase 2 studies. Patterns of liver function change are not readily identifiable

from these three studies because of different designs, different durations, different drug exposures, and different sets of tests completed in the studies. Even though it appears that the overall risk of hepatotoxicity may be low when midomafetamine is used, as it was in the phase 3 clinical trials, additional data could help to better characterize this risk.

We want to provide additional details about the abuse potential assessment for midomafetamine. Midomafetamine is currently a Schedule I controlled substance, and in that context it is better known as MDMA, ecstasy, or molly. Our controlled substances staff reviewed the published literature on midomafetamine, indicating some similar effects to other Schedule II stimulant class drugs associated with abuse potential with similar patterns of usage.

Given this history, we did not require additional human abuse potential studies but asked for more specific adverse event assessment, as discussed earlier. Because the systematic

collection of adverse events did not happen, our assessment of the rate of abuse potential adverse events remains limited. Thus, although we have enough information, based on a review of the published literature and epidemiological data to craft warning language related to abuse potential and prepare a scheduling recommendation for the DEA, we do not have information about the incidence of particular events that occurred in the clinical trials and will not be able to include those events in the adverse reaction section of labeling.

This lack of information also impacts our assessment of patient impairment. We know that the acute effects of midomafetamine result in changes in sensation, mood, and cognition that can last for several hours, but we have no trial-specific data to inform our characterization of the nature and time course of impairment for the proposed dosing regimen.

In MAPP1 and MAPP2, the protocol-specific observation period was 8 hours and discharge readiness was assessed per investigator judgment.

Nonetheless, most participants were discharged at the end of the 8-hour monitoring. There is an absence of data about specific symptoms or timing of symptom resolution to inform recommendations for any shorter time frame for monitoring.

Overall, the safety profile for midomafetamine observed in the development program is consistent with its known effects; however, certain risks cannot be fully characterized based on the safety data from this program. The assessment of cardiovascular risk, hepatotoxicity, and abuse-related adverse events did not adequately address these potential risks. In addition, because abuse-related adverse events were not captured if they were considered positive, favorable, or neutral, we do not have qualitative or quantitative information about the nature of the acute drug effects in this program or about when those effects resolve. As a result, we have limited information to determine appropriate discharge criteria for after the medication sessions.

Finally, we have a relatively small safety database in this program. This may be acceptable if we agree that the proposed 3-dose time-limited treatment is effective for the treatment of PTSD and that the treatment effect is durable. But if we determine that additional courses of treatment are needed, the safety database may not be adequate to characterize the risk of chronic or chronic intermittent use.

Having described the safety profile of midomafetamine, I want to turn now to our proposal for mitigating some of the risks associated with midomafetamine treatment. Many of the issues I have highlighted thus far could be addressed through postmarketing studies or product labeling if midomafetamine is approved. For instance, because it appears that the risk for hepatotoxicity is low if midomafetamine is used as intended, a requirement for a postmarketing study to further characterize midomafetamine's impact on liver function could be considered.

Elevations in blood pressure and heart rate

are time limited, and the product label can describe appropriate risk mitigation. For example, the warnings and precautions section of the prescribing information could describe the observed cardiovascular effects and advise providers to assess a patient's cardiovascular risk before prescribing midomafetamine and monitor heart rate and blood pressure during the medication session, ensuring that both have returned to safe levels prior to discharge.

However, midomafetamine is known to cause a variety of sensory and cognitive effects, rendering individuals in a vulnerable state for several hours. If midomafetamine is approved, we propose that a risk evaluation and mitigation strategy, or REMS, would be needed to mitigate the potential harms associated with this impairment. To provide an overview of the agency's proposed REMS, I will now turn the presentation over to Dr. Victoria Sammarco from our Division of Risk Management.

FDA Presentation - Victoria Sammarco

DR. SAMMARCO: Thank you, Dr. Millis.

Good morning. My name is Victoria Sammarco, and I work in the Division of Risk Management, and I will present FDA's thoughts on risk management for midomafetamine. I will begin with an overview on risk evaluation and mitigation strategies, or REMS, then I will discuss the risk for which a REMS is being considered for midomafetamine for the proposed indication. Then lastly, I will walk through the agency's proposed risk management through a REMS. We'll start with an overview of what a REMS is and what it may include.

A REMS is a drug safety program that FDA can require for certain drugs. REMS were enabled with the Food and Drug Administration Amendments Act of 2007, which authorized FDA to require application holders to develop and comply with REMS programs if it was determined necessary to ensure the benefits outweigh the risks of their marketed drug. REMS include strategies, in addition to labeling, to ensure that the benefits outweigh the risks, and they're designed to achieve specific goals to mitigate serious risks associated with the use of a

drug. REMS can be required pre-approval or post-approval.

REMS can include various combinations of components, which may include a medication guide; a communication plan targeting healthcare providers; certain packaging and safe disposal technologies for drugs if the REMS is needed to mitigate abuse or overdose; elements to assure safe use, or ETASU; an implementation system to guide operationalization of REMS requirements; and a timetable for submission of assessments of the REMS to ensure that the REMS is being assessed at appropriate intervals to ascertain whether the program is meeting its risk mitigation goals.

If deemed necessary, elements to assure safe use, or ETASU, will be included in REMS and can consist of certification and/or specialized training of healthcare providers who prescribe the drug; certification of pharmacies or other dispensers of the drug; limiting dispensing and administration of the drug only in certain healthcare settings such as hospitals or clinics;

requiring that the drug is dispensed or administered only with evidence of safe-use conditions; requiring that each patient using the drug is subject to certain monitoring; or requiring that patients are enrolled in a registry.

ETASU can impose burdens on the healthcare system and potentially impact patient access to treatment; therefore, ETASU are required if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate specific serious risks listed in the labeling.

I will now discuss the risk for which a REMS is being considered for this application. FDA is concerned about the known effects of MDMA, and by extension, midomafetamine, that may render the patient acutely vulnerable and cause serious harm. It's generally accepted that MDMA causes a temporary state that may include disinhibition and openness to suggestion or a range of intense emotions, as well as altered sensory perception and an impaired ability to perceive and predict motion.

The subjective effects may impair patients' judgment, which could lead to serious harm in the form of hospitalization, death, or events that could result in hospitalization, death, or with significant negative consequences.

The agency's rationale for our proposed REMS is again rooted in the patient impairment expected from midomafetamine administration and the need to ensure that patients are safe from serious harm from impairment. The agency's proposed REMS is informed by the strict controls that were in place during clinical development, which included that subjects were monitored in a controlled setting for an extended period, with overnight stays for most subjects after each medication session; that two therapists were required to be present during medication sessions; and that patients were instructed not to drive until the following day after medication administration. At this time, if approved, the agency believes a REMS will be necessary to ensure the benefits of midomafetamine outweigh the risk of serious harm resulting from

patient impairment.

I will now discuss the agency's proposed REMS. The agency's proposed REMS includes the following requirements: the drug be dispensed only in certain healthcare settings that can fulfill the REMS requirements; the drug be dispensed to patients with documentation of various safe-use conditions; each patient using the drug be subject to certain monitoring; and that each patient using the drug be enrolled in a registry to further characterize the REMS risk of serious harm from patient impairment.

In addition, the REMS would also include an implementation system to assist with operationalization of the REMS and a timetable for submission of assessments to stipulate that the REMS will be assessed, at minimum, at various prespecified times.

The goal of the REMS will be to mitigate serious harm resulting from patient impairment from midomafetamine administration by ensuring that during and after administration, patients are

managed in a medically supervised healthcare setting. The REMS will focus on mitigating serious harm, including, but not limited to, events resulting in hospitalization or death; events that could put patients at risk of hospitalization or death such as walking into traffic or driving while impaired by midomafetamine; events with significant negative consequences, including becoming the victim of a sexual assault or financial coercion; worsening of psychological disorders that cause disability or that may lead to hospitalization or death, including extreme anxiety or worsening of PTSD; and suicidal ideation and behavior.

The agency's proposed REMS will require that midomafetamine will only be dispensed in certain healthcare settings. REMS certified healthcare settings will be required to adhere to various safe-use and monitoring requirements in order to participate in the REMS and receive drug from wholesalers. Since midomafetamine will likely continue to be a controlled substance under the Controlled Substances Act if approved by the FDA,

healthcare settings participating in the REMS must additionally be licensed by the DEA to handle and dispense controlled substances.

Certified healthcare settings must have policies and procedures that support safe prescribing of midomafetamine within the setting, appropriate drug administration, patient monitoring throughout the time the patient is acutely impaired, as well as for direct patient follow-up soon after a medication session has occurred. Safety information collected during the medication session and after it must also be reported to the REMS to support the REMS registry and for compliance monitoring.

As part of the healthcare setting requirements under the agency's proposed REMS, certain policies and procedures must be in place to ensure safe use, though this list is not exhaustive. A prescriber must be available during midomafetamine administration and monitoring. At least two healthcare providers must be on site, with at least one being a licensed healthcare

provider, to monitor patient's medical status, including vital signs and psychological status for at least 8 hours and until the patient is stable to be discharged.

Emergency action plans must be in place to escalate care, if needed, based on changes in the medical or psychological status of the patient. Additional plans must be in place in case the patient requires monitoring for more than 8 hours. Policies and procedures must also be in place to assess that the patient is stable to be discharged from the healthcare setting and that the patient is released to an accompanying adult after each medication session. As a condition of healthcare setting certification, all relevant staff must be trained and agree to follow all established processes and procedures to comply with the REMS requirements.

Another requirement of the agency's proposed REMS is that patients will be enrolled in the REMS. Patient enrollment entails that patients will attest that they've been counseled on the

following: potential effects and risks of midomafetamine; the need to be monitored for at least 8 hours; the need to leave the medication session with an accompanying adult, and that they must also not drive or operate machinery until at least the next day; and they will need to follow up with the healthcare setting after each medication session. Patient enrollment also entails that they participate in a REMS registry described on the next slide.

Again, the agency's proposed REMS includes that each patient using the drug be enrolled in a registry. The purpose of the registry is to better characterize the risk of serious harm resulting from patient impairment. Data collected from the registry will also be used to determine whether changes to monitoring and other safe-use conditions in the REMS are needed. Examples of data collected include, but are not limited to, signs and symptoms of mental or physical distress experienced by the patient; onset and duration of short-term effects; monitoring duration; if care needed to be

escalated; and patient safety after medication sessions, including whether events indicative of serious harm from patient impairment from midomafetamine have occurred.

Though the REMS registry will provide data on all patients utilizing midomafetamine who are enrolled in the REMS, there will be limitations to this data stream since data may be incomplete for various reasons, including when patients are lost to follow-up. The REMS registry can also only be used to characterize the serious risk the REMS is intended to mitigate, which in this case, again, is serious harm from patient impairment associated with midomafetamine.

Lastly, the REMS will be assessed with a focus on measures that indicate if the REMS is functioning as intended and measures that indicate whether the REMS is meeting its goal of mitigating serious harm from patient impairment from midomafetamine. The REMS will be assessed according to the timetable of assessments, and findings from REMS assessments will inform if any

modifications to the REMS are necessary. Additional data sources such as through postmarketing requirements will additionally be used to fully characterize the risk and inform REMS modifications.

This concludes the agency's thoughts on risk mitigation through REMS at this time. Thank you, and I will now turn it back over for questions.

Clarifying Questions to FDA

DR. NARENDRAN: We will now take clarifying questions for the FDA. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know about the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

For panel members joining us virtually, please use the raise-hand icon in Zoom to indicate

that you have a question, and we will acknowledge you. Please remember to lower your hand by clicking the raise-hand icon again after you have asked the question.

Are there any clarifying questions for the FDA? The first question is from Dr. Dunn.

DR. DUNN: Walter Dunn, UCLA in the Greater Los Angeles VA. I'll start with two questions. Again, citing the recent ISA review about potential misconduct during the trial, specifically claimed that investigators discouraged people from participating in MPLONG; that therapists were encouraging reports of benefits and discouraging any reports of adverse events.

Is the agency investigating this?

DR. FARCHIONE: This is Tiffany Farchione. There isn't a lot that I can say with regard to specific details of what we're looking into related to the ISA report versus just our usual standard inspections. I think we're all aware of the report. We certainly take those allegations very seriously and are quite concerned by them. We do

have inspections ongoing at this point, but can't really speak to the details because those are ongoing.

DR. DUNN: Second question regarding the analysis of the MPLONG data, my understanding is that a tipping-point analysis with a shift parameter to penalize any patients who receive any interim treatments involving psychoactive substances such as ketamine or DMT were applied, and even after those penalties were applied, the data seems to be robust.

Based off of my interpretation of the briefing document, it seemed as if any additional psychotherapy or any additional use of traditional psychotropics such as SSRIs, that that shift parameter was not applied to those subjects. Number one, is that accurate? And number two, why wasn't that done based off the assumption that these subjects probably engage in additional therapy and restarted SSRIs because their symptoms either were relapsing or got worse?

DR. FARCHIONE: I can pass that to Dr. Yang,

or Dr. Morgan, if you want to respond.

DR. MORGAN: Hi. Olivia Morgan. So the question is, if we added a shift parameter to people who just received therapy but not with any other --

DR. DUNN: Right, either therapy or standard psychotropic medications, again, under the assumption that they're re-engaging in some type of treatment in the interim period because their symptoms are getting -- or they've relapsed.

DR. MORGAN: So we did apply the shift parameter to anyone who reported a psychotropic substance, which was ketamine, 5-MEO-DMT, or illicit MDMA, but not general therapy.

Someone else might be able to answer about how common if people are doing therapy, just regular therapy.

DR. FARCHIONE: We did have the slide up during the presentation about the intercurrent treatment, but if we don't have that data yet, we can certainly look into that and consider that as part of our future analyses.

DR. DUNN: My understanding of the shift parameter is, again, to, quote/unquote, "penalize" folks who receive some type of interim treatment under the assumption that they're getting worse so that you don't artificially inflate the durability of the effect. One of my comments would be that in addition to the psychoactive substances, any type of treatment that could be used to address a relapse of PTSD symptoms should probably be reanalyzed with that shift parameter.

DR. FARCHIONE: Yes, we can certainly do that.

DR. DUNN: Thank you.

DR. NARENDRAN: The next question is from Dr. Iyengar.

DR. IYENGAR: Satish Iyengar from University of Pittsburgh. I have a question for Dr. Morgan. One of the things that Dr. Millis mentioned was the heterogeneity among the therapists. Is an analysis that uses therapists as a potential random effect or something like that possible here, or is it complicated by the fact, by the possibility, that

it's not just the therapist, it's the therapist along with the patient interaction, and that's what matters? At least to get some rough idea of is there a therapist heterogeneity effect; is that kind of analysis possible?

DR. MORGAN: Thank you for the question. Well, the models did adjust for site, so assuming that the same therapists were at the same site, that might be partially accounted for, but I'm not sure if there's multiple therapists at each site. We can look into that, and that's a good idea. Thank you.

DR. IYENGAR: Thank you.

DR. NARENDRAN: Just related to that, I'll just add in, I was also looking at the sponsor slide that looks like more people on MDMA went back on ADHD psychostimulants, so maybe that's something to look at and add in the shift parameter analysis because twice as many looked like they were on psychostimulants for ADHD.

DR. NARENDRAN: The next question is from Dr. Holtzheimer, who's virtual.

DR. HOLTZHEIMER: Thank you. Paul Holtzheimer, National Center for PTSD. This relates to my earlier question to the sponsor. In addition to the potential concerns with the functional unblinding in these studies, there's the concern that the therapists themselves were unblinded, which led to my earlier question about could there be systemic differences in the psychotherapy delivered in the two arms, so that the therapists who are unblinded might treat the patients that they think have the psychedelic on board differently than the patients who have placebo on board. When I posed the question to the sponsor earlier, the answer was that there was assessment of fidelity and adherence, and that there were no noted differences between the two arms.

I am curious if the FDA received those data and what the FDA's assessment of the maintenance of integrity of the psychotherapy was between the two arms; again, recognizing that psychotherapy is sort of outside the scope of the FDA but, again,

critical to this application.

DR. FARCHIONE: I would say that based on the description of the therapy in the manual and -- how should I put this? -- the flexibility inherent in the manualized psychotherapy, we assumed that there would be variability among the different therapeutic approaches. Now, whether that was specifically related to if there was some ability to detect or guess the treatment assignment, we don't have any assessment of that.

DR. HOLTZHEIMER: Thank you.

DR. NARENDRAN: The next questions from Dr. Rebo

DR. REBO: Hey. Elizabeth Rebo from Kaiser Permanente. I have a couple questions about REMS, and I'll ask them one at a time. The first was around the patient being agreeable to monitoring. I'm wondering if you can expand on what that means. Is that just basic monitoring during the session, doest that include labs, or has that not been defined yet?

DR. LaCIVITA: Hi. Cynthia LaCivita, FDA.

The patient monitoring would be the agreement that they understand. They'd have to be monitored for 8 hours, so after they take therapy. So it's those types of conditions that they would need to agree to.

DR. REBO: Okay, so no pre-, post-labs, any of that would not be included, or has that not been defined?

DR. LaCIVITA: That has not been decided, no.

DR. REBO: Okay. And then my second question was around the healthcare setting requirements. The list in the PowerPoint said that it's not exhaustive. What else would it possibly be? Is that left up to the facility? How is that decided?

DR. LaCIVITA: Those are still under consideration within the agency and, of course, in discussions with the applicant; but certainly if you have anything you'd like to suggest, please do so.

DR. REBO: Okay. Thank you.

DR. NARENDRAN: Our next question is from Dr. Joniak-Grant.

DR. JONIAK-GRANT: Hi. Thank you. I have a question. In looking at the information from the sponsor, they note that they'll require enrollment in their therapy training program, which hearing about all this flexibility, and this therapy manual, and things like that, certainly as a patient makes me uneasy. It sounds like it could be like whatever we think it should be.

FDA is not, from what I can tell, requiring a type of training like that. Could you speak more to that? Basically, I'm trying to ascertain -- it seems like on one hand, Lykos is saying it's going to be very controlled within our system and done our way, and FDA on the other hand is saying we're going to move it into perhaps; and I may be misunderstanding other healthcare settings with a little bit more leeway of what the therapy portion could be.

DR. FARCHIONE: Well, the difficult thing, and something that you've just hit on very well, is

that we don't regulate psychotherapy at all, so we don't really have any say in the design or the implementation of the particular therapy that is going to be used. We can say, generally, that this is something that would need to be administered in conjunction with a psychological intervention, but that's really the extent of what any labeling language would suggest. And even when it comes to the parameters of the REMS, those are focused on safety and monitoring, not on the intervention that would occur at the time.

DR. JONIAK-GRANT: So would FDA have the ability to say, for example, that this therapy training program is not required?

DR. FARCHIONE: We wouldn't have any comment on that.

DR. JONIAK-GRANT: Okay. So that could be required by Lykos.

DR. FARCHIONE: I mean, I guess it could be --

DR. JONIAK-GRANT: Okay.

DR. FARCHIONE: -- but it wouldn't be a

requirement that we would implement.

DR. JONIAK-GRANT: Understood.

Then one other thing; if inspections to investigate these claims are ongoing, is it possible that this could come to market, if it is approved, before these inspections are completed?

DR. JONIAK-GRANT: I'm sorry. Can you repeat that?

DR. JONIAK-GRANT: You mentioned earlier that inspections were ongoing into some of the claims about data manipulation and such. Is it possible, if things were to be approved today, that it could come out to market before those inspections are completed?

DR. FARCHIONE: Sorry. I keep forgetting to introduce myself before I speak, but Tiffany Farchione again. We would complete the inspections before taking action.

DR. NARENDRAN: Our next question is Dr. Hertig.

DR. HERTIG: John Hertig. I recognize in advance I'm going to ask a question that there may

not be a great answer to, but I'm going to ask it anyway.

In looking at the burden of disease with regards to PTSD and the impact this could have on that burden, I'd like to try to get a sense for whether the agency has any comment on the accessibility here, because after the REMS programs, related mitigations, the limited rollout, the controlled access and distribution pathways, exclusion criteria, including those patients that have cardiovascular disease, I'm trying to get a sense for after we do all these things, how many of these patients are actually going to have access?

So I'm just curious whether there's any insight or thought on that particular question. Thank you.

DR. FARCHIONE: This is Tiffany Farchione again. You're right; there isn't a good answer. We don't have an answer to that. We can't really predict that. But in terms of trying to design a REMS that can appropriately mitigate the risks that we've identified, we have tried to think about

patient access as well. The last thing that we want is to make that REMS unduly burdensome to the point where folks who could benefit from the drug are not able to do so, but at the same time, we do have a lot of unknowns and we do have some clear risks with this product.

So the best that we can do is try to balance all of those considerations to ensure that we have appropriate elements to assure safe use, but that's not unduly burdensome. And, of course, we do periodic REMS assessments as well, so that does also open up the opportunity to modify the REMS at some future date, based on new information as well.

DR. NARENDRAN: Our next question is Ms. Witczak.

MS. WITCZAK: Kim Witczak, consumer rep. I know that you do not regulate psychotherapy, but when we get into postmarket, even people reporting into MedWatch, is there a way that we are going to be able to -- and they report something, and it's maybe not drug related, it's partly therapy related, how are we going to be able to separate

that and do something about it versus is this drug related, is this therapist related?

Again, it goes back to we don't regulate therapists, because then when you put all the REMS in, I'm wondering do you all of a sudden have the breakthrough, all the hype for it, that people then will go and use street drugs for it. It's part of that whole safety part of it with how the psychotherapy part of it is not in there, and that's out of your purvey.

Is this an opportunity that we can maybe do something a little bit different at the FDA, and bring in a committee, and bring in somebody, bring in experts that can actually help identify it? Are we looking at this drug approval through the eyes of a typical approval when there are so many other issues? We keep hearing that we're limiting, and it could be potentially access to patients, and it could be therapists.

So those are just some questions, and I would love to have somebody answer, and it might be too early that I'm asking these.

DR. FARCHIONE: Again, this is Tiffany Farchione. So a couple of things; when it comes to some of the risks, like you were saying if something happens in the psychotherapy, one of the reasons -- with the certified healthcare setting, the providers to be involved in delivering care -- to have that requirement for independent licensure is so important because then the oversight of that individual is going to fall to state medical boards and other licensing bodies. People lose their license if they engage in malfeasance of some kind, or misconduct with a patient who's in their care, not to mention the potential for criminal charges and all of those things.

Not everything has to be managed by the FDA. There are other bodies that can handle those aspects of it; but again, ensuring that the person who is delivering the treatment; that at least one of those individuals is licensed independently should help with that.

In terms of this thought of engaging experts

and asking for advice, that's why we're here today. We really want to hear from everyone on this panel. We're looking forward to the open public hearing to hear from individuals affected by PTSD or who potentially have been part of these trials, to get more information and to be able to incorporate that into our decision making as best we can. This is something unprecedented, so we certainly want to get as many opinions and as much input as we can on this product and on our decision making.

MS. WITCZAK: Yes, because I know there are a lot of other investigations out there within the psychedelics, so I really think we're charting new territory. So are there other -- when I say experts, I mean, obviously, this group is full of experts, but those that are actually doing other psychedelic investigations, et cetera, just because I think we are charting new territory and we want to set it up right, so thank you.

DR. NARENDRAN: Our next question is from Dr. Amirshahi.

DR. AMIRSHAHI: Hi. Maryann Amirshahi,

Georgetown. One of the questions/ comments I had was regarding the laboratory assessment. I think we focused a bit on the potential for hepatotoxicity, which I think is fair, but one of the things that we didn't discuss so much is the potential for hyponatremia, and traditionally we do have concerns about that, particularly with MDMA.

The issue is, I recognize that these patients that are undergoing this therapy are not going out to rave parties all night, but we do have a large number of patients that may qualify for this medication that have relatively well-controlled comorbidities, such as CKD or mild hypertension, and diuretics are very, very commonly used, and those may predispose patients to hyponatremia. So I think the data that we have on this is more in the setting of an acute or illicit overdose, in a completely different setting, and I don't think that that has been adequately explored.

So I would just like to ask, number one, do we have a plan for that, and if not, I'd like to make a plug for it. Thank you.

DR. FARCHIONE: Tiffany Farchione again. We are considering what kinds of postmarketing requirements, and that's important to note; that when it comes to evaluating safety issues in the postmarketing session, we can require those studies. They're not just commitments; they are actual requirements with deadlines and everything.

We're looking at potential postmarketing requirements, both for clinical laboratory assessments -- not just for liver function, but all clinical labs, and we're also looking at additional data that we could assess for cardiovascular safety, but the exact design of those studies hasn't really been settled yet. But we do think that having a separate stand-alone study, not just gathering data through the REMS or something like that, would be important, especially because of the amount of time it would take to gather that information through the REMS versus just a quick stand-alone study on its own.

DR. NARENDRAN: Our next question is from Dr. Barone, who's virtual.

DR. BARONE: Hi. Melissa Barone, VA Maryland Health Care System. My question is with respect to the psychotherapy part of the treatment. The therapy is described in the briefing documents as being a critical component to the treatment. The MDMA is not offered without the therapy; that's not an option. The therapy approach is described as whatever the therapist is familiar with, and that's not consistent with clinical practice guidelines for PTSD. It's not consistent with the existing evidence-based treatments for PTSD.

I understand the FDA is not responsible for approving the therapy approach, but given that it isn't consistent with the clinical practice guidelines, what would be the process, then, for approving the therapy part of the treatment, like I said, given that it hasn't been a approved yet? And I'm sorry if there's not a great answer to that question. Sorry.

DR. FARCHIONE: This is Tiffany Farchione again, and there is not a great answer to that question because, again, even if there was a study

looking specifically at the psychotherapy itself, that's not something that would fall under our purview. So in terms of approving a particular psychotherapy, that's not something that we would do.

DR. BARONE: Thank you.

DR. NARENDRAN: Next question is Dr. Dunn.

DR. DUNN: Walter Dunn, UCLA, VA, a couple of questions. How does the FDA view that phase 2 trial incident where there was inappropriate criminal transgressions that occurred long after the last dose of MDMA was delivered? In the presentation, there's discussion about patients being acutely vulnerable; however, given the nature of that drug being pro-affiliative, prosocial, breaking down barriers, one could say that that sexual relationship that took place in the phase 2 trial began in that MDMA session.

Is that something that you'll be monitoring, number one? Number two, would that be considered an adverse effect of the MDMA given that it happened weeks after the last dose was given?

DR. FARCHIONE: Tiffany Farchione again. I think that this is an area where it would be really useful to hear from the committee in terms of how we might be able to incorporate that into our REMS structure. In terms of the time frame of that and looking that far out from the session, the further out you get from the session, the harder it's going to be to attribute that directly to the drug effect, but any suggestions that you might have for additional monitoring or anything along those lines would certainly be welcomed.

DR. DUNN: And second question, there's been a lot of discussion about psychotherapy not being in the purview of the agency, but it's been discussed primarily in the context of efficacy. Again, this is a hypothetical question, but if the sponsor, or other additional trials, investigations, conclude that this particular psychotherapy that is being promoted by Lykos, for whatever reason, ensures a greater safety margin than our typical more directive psychotherapies, hypothetically, could that be included in a REMS if

it's shown that their psychotherapy results in less adverse effects than more directive trauma-focused therapies?

DR. LaCIVITA: Hi. This is Cynthia LaCivita, FDA. That is something that we'd have to look into. This is very unusual for us.

DR. DUNN: And third question, in terms of the licensure issue, so why only one licensed therapist? We're dealing with a fairly severe population. This is, I think for all intents and purposes, a fairly invasive treatment. What was the rationale in terms of having only one licensed therapist in the room? Why not have both be licensed therapists?

DR. FARCHIONE: Tiffany Farchione again. In the clinical trials, we've only required one of the two monitors to have a license. What we have asked for the second monitor is at least a bachelor's level degree and some experience in a mental health setting, and so on. It primarily has to do with the concerns of balancing access as well.

DR. DUNN: Again, reminding folks that that

transgression happened with an unlicensed therapist in the phase 2 trials. And again, thinking about clinical rollout, I know the sponsor mentioned that they would allow therapists who are in training, but again, thinking about -- how should I put this delicately? -- for-profit operations which may misrepresent the training status of people who are unlicensed, saying that they're potentially in training when they're actually not just to use the least resource-intensive personnel for their treatment, perhaps there needs to be, or can be, more delineated guidelines as far as what that second therapist can be. My personal feeling is that both should be licensed, but that's for further discussion, I suppose. Thank you.

DR. NARENDRAN: Our next question is Dr. Joniak-Grant.

DR. JONIAK-GRANT: Thank you. I actually wanted to comment as well on the licensure. I think it's important for FDA and people to remember that, oftentimes, if you have one person who's licensed and another person who is not, a patient

will tend to see it as that person is their advocate, so if something is going wrong or awry, someone would speak up on my behalf. If person A is doing something wrong, person B would speak up on my behalf.

When you don't have people of equal status in that relationship, that can cause all kinds of problems when you get power imbalances and hierarchy. I'm thinking about, what if you have a senior professor, and you have somebody who's a graduate student who's in the process, they're going to call them out. And there are tons of instances of residents and fellows calling out bad behavior by clinicians all over the U.S., and nothing being done, and nothing being investigated for years and years and years. So I think we have to really think long and hard about that. I definitely hear what everyone is saying in terms of access, but it is a balance.

The other thing I wanted to mention was talking about people being on site. That seems very, very broad to me. I have gone in for

different treatments or infusions, and there's somebody on site, but they might be a 5-minute walk down the hall, go up an elevator, turn around. I had an allergic reaction once to an infusion, and part of that reaction was to not really care. So people just kept wandering past me, and CMAs were wandering past me. And then my husband came in from the hall and looked at me and said, "What's going on here?" He had to go get someone. So the idea that people can just sort of be around is not necessarily going to be protective enough for patients. I'm done.

DR. FARCHIONE: This is Tiffany Farchione again. Just to respond to that, I can say that in the clinical trials, what we've typically asked for in just psychedelic programs in general is to have the two therapists either in the room or to have someone observing remotely but on site, whether it's video monitoring or something, something where if they see something happening, it's live monitoring and they can intervene. The only time that folks are left alone is for a short bathroom

break or something like that.

I can defer to Dr. LaCivita in terms of how stringent we may be able to be about similar requirements in the REMS for the healthcare certification perhaps, but it's certainly something that we can take under advisement.

DR. NARENDRAN: The next question, Dr. Canuso.

DR. CANUSO: Carla Canuso, industry Rep. So I understand that there will, you know, be a postmarketing requirement for laboratory assessments, but how is it there was not a requirement for laboratory assessment at the time of submission?

DR. FARCHIONE: Yes. Again, this is Tiffany Farchione. It was missed. It was missed. It's one of these things that every program that we ever review always has labs, and I think that perhaps the primary reviewer, the person reviewing the clinical study, because it's always there, just didn't notice that it wasn't. It is a hole in the program that I think both the applicant and we have

to take responsibility for.

DR. NARENDRAN: The next question is Dr. Holtzheimer, who is virtual.

DR. HOLTZHEIMER: Hi there. Again, Dr. Holtzheimer, Paul Holtzheimer, National Center for PTSD. I apologize for this, but there was a slide on high expectancy, low expectancy, and the difference between active and placebo. Is it possible to navigate back to that slide? I had a couple questions just to make sure I fully understand what it's showing.

DR. FARCHIONE: That was one of the applicant slides, right?

DR. HOLTZHEIMER: I think it was in the FDA presentation.

DR. FARCHIONE: No, that was during the Q&A for the applicant.

DR. HOLTZHEIMER: Okay. Sorry. I missed that. Obviously, expectancy bias is my potential issue here, and I guess I'm questioning how the FDA -- again, you're asking us to review that, and I appreciate that, but how is the FDA looking at

that? My understanding of that earlier slide was that expectancy was not measured before in the treatment; it was somehow measured during the treatment or maybe after. High expectancy, there was not a difference between active and placebo; low expectancy, there was a notable difference.

Does the FDA incorporate -- I guess maybe the question is, statistically, do you somehow find a way to incorporate that or how does that mitigate your understanding of the results?

DR. FARCHIONE: Yes. Tiffany Farchione again. Statistically, no. I mean, really, what we're trying to do, and what we're hoping the committee can also comment on, is we're trying to qualitatively assess how much we, quote/unquote, "buy" the results in the context of all of this expectancy and unblinding.

Again, there are measures in place to potentially mitigate that through the blinded central raters, but the fact is that you just can't blind these studies, so what do we do with that? And, obviously, we're considering it from all

angles, and ultimately when we do ask you on the first voting question what you think about that, you'll be taking that into account as well.

DR. HOLTZHEIMER: Then, a different question --

DR. BURACCHIO: Oh, I was going to add on to that. This is Teresa Buracchio, Director of the Office of Neuroscience. We know that there is expectation bias and functional unblinding in this study, and it was something that we anticipated at the time of the review of these protocols. It was something that we actively discussed with the applicant during the special protocol assessment.

We're not surprised by the results of the functional unblinding study. It is something that was anticipated. When we think about how to handle this, we know that there is bias to these studies, and we have to factor that into our consideration of the results. And how we tend to think about how to handle bias when we're looking at the results is some of the things that were mentioned in the comments by Dr. Farchione in the opening comments.

We want to look at the magnitude of the effects. We want to see are the effects of the studies robust, persuasive, and are they consistent across endpoints. Do we feel like the results are large enough and compelling enough that they may be able to overcome the biases that we have identified in the study? As experts in PTSD, some of the things that would be helpful for us to know is when you treat patients who have PTSD, what are your expected results with standard therapies, and do these results appear to exceed what you typically experience? Are they consistent with what you typically experience?

So we have our thoughts on how to consider bias in the interpretation of these results, but we really do want experts in PTSD to help us understand how do you view these results, knowing that there are biases, but do you find them compelling or persuasive regardless of those of those biases?

DR. HOLTZHEIMER: Thank you.

Then a separate question, in the long-term

follow-up data, my recollection of the slide that the FDA reanalyzed the data with the interim-use subjects treated as missing and the modified intent-to-treat sample, that the MAPP2 outcomes was basically non-significant at endpoint between the active and the placebo group.

Am I correct in that interpretation?

DR. FARCHIONE: No. I'm not sure what you were -- do you know what slide?

DR. HOLTZHEIMER: So there was --

DR. FARCHIONE: Do you have a slide number that we could bring back up?

DR. HOLTZHEIMER: It was the reanalysis of the MPLONG study. Let me see if I can find it in my slide deck.

DR. FARCHIONE: Slide 39?

DR. HOLTZHEIMER: Possibly.

DR. FARCHIONE: Can we bring up slide 39?

DR. HOLTZHEIMER: My slide is slide 57 of 92. Would that make sense?

DR. FARCHIONE: The one that's on the screen, is this what you're talking about?

DR. HOLTZHEIMER: Yes, that's the one.

So I'm looking at the bottom right-hand corner. This is the modified intent-to-treat sample imputing all missing data under missing at random, and I'm looking at the estimates for the active and the placebo groups. Both of them cross 0, so my interpretation of that is that there was not a significant difference in long-term efficacy between those two groups.

(Pause.)

DR. HOLTZHEIMER: Yes, I guess I'm asking if that is correct.

DR. FARCHIONE: Sorry. I'll pass this to Dr. Morgan.

DR. MORGAN: Hi. This is Olivia Morgan. These results here, it's the difference from the long-term follow-up visit minus visit 19; so we're looking at the change between the parent study and the long-term follow-up. When looking at this long-term follow-up, we're not really comparing treatment to control because there was a different estimate at week 18 at the end of the parent study,

so we're looking at the difference from week 18.

DR. FARCHIONE: Yes, if I can clarify a little further. If you look at the top line, you might think that even after the end of treatment, getting no additional doses of medication, it seems in both MAPP1 and MAPP2 that, potentially, the individuals who had received midomafetamine in the parent study looked like they continued to improve a little bit, whereas placebo stays flat; whereas in the additional analyses, that's less clear. And again, in MAPP2, it kind of looks like both slightly improved about the same amount. So again, there is a difference still in the parent study, but this is continuing on with no additional treatment.

DR. HOLTZHEIMER: And I apologize. Again, I've been trying to follow along here, but since one of the questions is durability of effect, I'm trying to clarify what data the FDA received to show that the MDMA-assisted psychotherapy had a durable effect over time.

DR. FARCHIONE: And again, Tiffany

Farchione. That's what this data is. So again, no additional treatment, what happened to the scores from the end of treatment to the follow-up visit; so six months later, you're still seeing either similar or slight improvement in the MDMA group.

DR. HOLTZHEIMER: Okay. Thank you.

DR. NARENDRAN: Just a couple more minutes, so, Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA, VA. Two questions, and then this might be actually for the sponsor after lunch. My understanding of the trial protocol is that subjects were permitted to have additional therapy sessions beyond the three integration sessions after each of the medicine dosing. Does the agency have any data as far as how many extra hours of therapy the MDMA arms received compared to the placebo arms?

DR. FARCHIONE: I think that's probably a question for the applicant.

DR. DUNN: Okay.

The second question, would you consider a warning label for the therapists? And let me

explain. Obviously, this is a fairly unique treatment with the effects of the drug, and I think the sponsor would agree that the therapists in the room are experiencing something that for themselves is a non-ordinary interaction with the patients.

Obviously, we know that in psychotherapy, counter-transference from the therapist plays a big part. This is probably going to be enhanced for somebody under the influence, or acute influence, of MDMA, and I'll cite the preclinical studies from one of my colleagues at Stanford, where they showed that you've got two mice. One is dosed with MDMA, one is not. The mouse that is not dosed behaves differently in the presence of the mouse dosed with MDMA. I believe the measures they use were not technically statistically significant, but there was a trend that that other mouse was acting differently.

Obviously, hopefully our prefrontal cortex is more developed than that of a mouse, but is this something you would consider in your warning labels given, again, that in the underground, and even

during the clinical trials, ethical and boundary violations did occur?

DR. BURACCHIO: Hi. This is Teresa Buracchio, Director of the Office of Neuroscience. I think for a warning, the warnings or prescribing information is typically directed toward the prescriber, not necessarily toward the therapist, unless the prescriber and the therapist are the same; however, we can describe in a warning what the perceptual changes might be that could be expected.

A therapist who is doing this, even though the prescribing information is directed toward the prescriber, I would think that a therapist should also be familiar with the prescribing information, so I think we can't necessarily give directions to the therapist, but we can describe the perceptual changes and sensory effects that may occur that could influence the relationship with the therapist.

DR. DUNN: Alright. Thank you.

DR. NARENDRAN: One more question from

Ms. Witczak.

MS. WITCZAK: Kim Witczak, consumer rep. Do you consider this a robust number of people? As you're starting to look at psychedelic trials, is under a hundred people for a disease at 13 million, is that considered -- that got the actual treatment? I'm just curious for your thoughts on the total numbers in this trial that actually got the drug plus therapy treatment.

DR. FARCHIONE: Tiffany Farchione again. If this were something that needed to be administered on a more frequent basis, something that would be considered either chronic treatment like the daily dosing that we do for SSRIs, or even chronic intermittent, where you give it every few days to a few weeks, or something like that, we don't really have a dividing line between chronic and chronic intermittent where we have a cutoff. But if that were the case, we would expect more data, primarily to have more safety data.

But in terms of the number of folks who were dosed using this paradigm in the short-term studies

for an indication for a single use, it does appear that the effect is robust, it's statistically significant, it's clinically meaningful, and it was seen in both studies.

DR. BURACCHIO: I can add that for an efficacy evaluation, the size of the studies is really based on the power calculations and the number of subjects that you need in order to demonstrate an efficacy signal. We don't have a set number of subjects that are required in order to establish efficacy. We do have requirements for safety, as Dr. Farchione just described; however, I think if these are large enough effects, you could do a smaller study. I think in psychiatry trials, in general, it's usually a few hundred patients or so.

DR. FARCHIONE: But that's also because the effects are smaller.

DR. BURACCHIO: Yes, and the effects are smaller, so they require a larger sample size.

DR. NARENDRAN: One last question for myself, Raj Narendran. One of the things that I

struggle with is there's a lot of missing data. There's no discharge EKG. Blood pressure was measured, heart rate was measured 3 times during a session at baseline, 1.5 hours in a discharge, and there were no laboratory values collected with liver.

One of the things, people with borderline hypertension were probably dosed 140 over 90, which is not something typically I would consider doing. With the REMS, can it say do not dose people over 125 over 85; heart rate has to be between this and this; collect blood pressure and heart rate maybe every 15 minutes until discharge, and can you do a discharge EKG? Would you be able to -- the lack of data, is it just ok, it's fine, we did 100 subjects, it looks great, or can you restrict them more in terms of medical safety?

DR. FARCHIONE: This is Tiffany Farchione again. I can start, and then Dr. LaCivita can comment on what we can and can't do. It's certainly something that we could consider. If the committee were to say, "We're really concerned

about these cardiovascular effects, and we think that they haven't been adequately characterized, and we think that you need something in place to mitigate that," it's something that we could consider.

Dr. LaCivita, if you want to talk about the kinds of things that could be included?

DR. LaCIVITA: Cynthia LaCivita, FDA. I think we'd like to hear your suggestions on that, but it's certainly something that we can consider. And whatever we're going to be collecting in the REMS is going to have to be reflected in the labeling also, so these are going to have to be risks that are identified in labeling so that we can address them in the REMS.

DR. NARENDRAN: I think we're a little past time, so we'll now break for lunch. We will reconvene again in this room at 2:00 Eastern Time. Please take any personal belongings you may want with you at this time. Panel members, please remember that there should be no chatting or discussion during the lunch break. Additionally,

you should plan to reconvene at around 1:50 pm to ensure you are seated before we reconvene at 2:00. Thank you.

(Whereupon, at 1:11 p.m., a lunch recess was taken, and meeting resumed at 2:00 p.m.)

A F T E R N O O N S E S S I O N

(2:00 p.m.)

Open Public Hearing

DR. NARENDRAN: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do

not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have three minutes.

MR. DEMPSEY: Good afternoon. My name is Brian Dempsey. I represent Wounded Warrior Project and have the privilege of serving as the organization's Director of Government Affairs. Our organization's mission is to honor and empower wounded warriors, and we do so with a particular emphasis on those who served on or after September 11, 2001. With that community in mind, I'm grateful for the opportunity to speak to you about our views on mental health care and the positive potential of expanding care options through wider adoption of MDMA-assisted psychotherapy.

Our perspective is shaped by how we serve. More than 200,000 warriors have registered with Wounded Warrior Project, and while many seek initial help with obtaining VA benefits or finding social connection in their community, our largest programming investment is in mental health. Our mental health continuum of support is a series of programs that address veterans' mental healthcare needs, and its goal is to connect veterans with the

appropriate amount of care they need to get to their highest possible level of resilience, psychological well-being, and healing.

We learn a lot from warriors when they first reach out to us and as we assist them throughout their care journey. As roughly 9 in 10 warriors we serve use VA for health care, many started there. To be clear, VA delivers excellent care, but negative feedback about long wait times, provider churn, and emphasis on prescription medication are not unique.

Warriors will often come to Wounded Warrior Project because we can help connect them to care sooner and have innovative programs like our Warrior Care Network and Project Odyssey that offer unique ways of bundling clinical and nonclinical mental health support that offer fresh hope for improvement and recovery.

All of these points underscore how increasing demands, unique interaction with the healthcare system, and willingness to try new approaches when others aren't working are extremely

present factors for veterans suffering from invisible wounds of service. To quote one of those veterans that we serve, "In my honest opinion, it was not --"

Hello?

DR. FRIMPONG: Hello. This is the DFO. We can hear you ok, speaker number 1. You can continue.

MR. DEMPSEY: Okay. Sorry. There was interference from another broadcast of it. I apologize greatly. I'll resume at the beginning of the quote. I'm sorry for the interruption.

To quote one of those veterans that we serve, "In my honest opinion, it was not until I also utilized non-traditional methods of treatment that I was finally able to feel consistent, prolonged relief between treatments. The best way that I can explain this treatment is a perspective switch. Forming new neural pathways helped change the way I viewed my situation, fueled my desire to continue treatment, and facilitated continued follow-up as time between treatments increased.

"Psychedelic-assisted therapy is not the answer alone and requires work on the part of the person being treated; however, it is definitely a step in the right direction."

We believe there are still important considerations about patient education, treatment scalability, and impact unemployment that need to be addressed, but we are wholly committed to finding new options for care for veterans who want and need care that they deserve. MDMA-assisted psychotherapy for PTSD has shown great promise in multiple studies and is safe when used in clinical trials.

Approximately 29 percent of the post-911 veteran population experiences PTSD, and with the pronounced impact it can have on quality of life and suicidality --

DR. NARENDRAN: Speaker number 1, your time is up.

MR. DEMPSEY: -- giving veteran's hope and avenues to effective treatment are among our highest priorities for those we serve. Thank you

for the opportunity today.

DR. NARENDRAN: Thank you.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and organization for the record. You have three minutes.

DR. GRANT: I am Robert M Grant, a practicing physician, a professor of medicine at UCSF, and a former chief medical officer for a large aid service organization. I received funding from the sponsor for research more than two years ago, but have not received any funding in the last two years or for my participation today. I have 40 years of experience with HIV research and pulmonary and critical care medicine, and to the advisory committee, I've been in your shoes, having served on an FDA advisory committee through four new drug applications, including two first-in-class.

I became trained in MDMA-assisted psychotherapy because I'm aware of how PTSD drives

enormous suffering on its own and that PTSD is also an underlying driver of many medical and surgical diseases. For example, I work in an intensive care unit at a large public hospital in San Francisco. After every shift, I walk around my ICU and ask myself, "What proportion of my critically ill patients are there because of underlying PTSD that is untreated or undertreated?" Some days I count 100 percent: liver failure due to alcohol abuse, due to PTSD; pulmonary or cardiac failure due to tobacco, due to PTSD; sepsis due to injection drug use; cardiac arrest due to fentanyl; trauma due to violence; undiagnosed HIV due to stigma; suicide attempts; it goes on and on.

PTSD is an underlying driver for much of our disease burden broadly, and existing therapies for PTSD are relatively ineffective and poorly tolerated, with less than 5 percent of the affected population being willing to start and complete the current standard of care.

Today, you've seen evidence that MDMA-assisted psychotherapy is safe and effective

for treatment of PTSD. I find that evidence to be convincing and compelling, especially when combined with the substantial phase 2 program that has all been published and is presented in your packet, although just not discussed in detail during this meeting.

I'm especially impressed with the sponsor's rigorous use of blinded independent raters to evaluate mental health outcomes which are inherently subjective. The REMS proposal seems reasonable, and REMS never eliminate risk and never eliminate the need for peer supervision, licensing boards, and patient advocacy.

I ask you to seriously consider the evidence for MDMA in the light of enormous unmet psychiatric need, and even larger unmet medical and surgical needs that could be mitigated by a more acceptable, better tolerated, and highly effective treatment for PTSD. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 3, please unmute and turn on your webcam. Please introduce yourself. Please

state your name and organization for the record. You have three minutes.

MR. HAUSFELD: I'd like to thank the FDA for the opportunity to provide comment today. My name is Russell Hausfeld, and I have no conflicts of interest here. For the last eight years in my capacity as a journalist, I have followed the developments of the sponsor organization Lykos Therapeutics, or as it was known until earlier this year, MAPS Public Benefit Corporation.

When I initially began covering Lykos, I thought I was aligned with the goals to legalize and destigmatize psychedelics. After years of reporting on Lykos, however, I now fear that it would be irresponsible to endorse this company to roll out a radically new pharmaceutical and therapeutic intervention to the world.

Over the last eight years, I've been demonstrably lied to by Lykos' team on multiple occasions. I've fielded disclosures of sexual abuse that happened on Lykos' watch. I've observed gross mishandling and misrepresentation of clinical

trial data. I've seen evidence that leadership sexually and financially exploited donors, and I've cataloged Lykos' long-term strategy to mainstream with interventions through appeal to the VA and the DoD, while simultaneously exploiting its own volunteer veterans.

Because the political strategies of Lykos have largely revolved around centering veterans in public relations, I wanted to highlight the words of some of the vets who volunteered with Lykos and whose stories of mistreatment I cataloged during reporting I conducted in 2022.

One military police veteran worked with Lykos and told me, "I watched as Lykos and its researchers used veterans up and discarded them as soon as they no longer served a useful purpose, regardless of mental health consequences or social implications."

One Navy veteran told me of a number of instances in which he felt veterans were paraded around, used as props, and exploited for free labor, and a Marine veteran felt that the company

leadership essentially stole his research and kicked him off of his own project, saying, "If this mistreatment by Lykos is happening to me, it concerns me about the population that Lykos will be working with moving forward. Working with Lykos has been very, very crushing to me as an individual and as a veteran." Further details about these stories can be found in my written comment on the FDA website.

In conclusion, I agree with these veterans who worry about the incredibly vulnerable patients that Lykos intends to work with if it receives approval for MDMA-assisted therapy. The organization has demonstrated time and time again that it is willing to play fast and loose with data and with people's lives. I do not trust Lykos to spearhead a new industry of psychedelic pharmaceuticals, and I ask that the FDA think hard on the potential consequences of allowing this company to move forward with approval. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 4, please unmute and turn on your webcam. Please introduce yourself. Please state your name and organization for the record. You have three minutes.

MR. TYLEK: Hi. My name is Casey Tylek. I have no financial interest in this at all. As a veteran who has served in Iraq for 15 months with the United States Army, a victim of an armed robbery, and someone who partakes in an extreme sport where serious injuries and deaths happen frequently, I have lived with PTSD most of my adult life.

My symptoms of PTSD have manifested mostly in angry reactions, fear and anxiety, nightmares, and a lack of compassion for others. It has made my life very difficult with friendships, relationships, and my jobs seemed destroyed in the process as a result of some of these reactions. I have seen these same effects of PTSD of my fellow veterans and the resulting life struggles, and all too often I've read about a friend ending their own life because PTSD has destroyed all humility in

their life. I, too, have had that thought constantly.

I tried a number of therapies, techniques, medications, and self-help books to overcome this. Very few of them had any lasting effect and they weren't very meaningful. Being frustrated with this, I pretty much gave up on focusing on treatments because I felt they were pointless and ineffective, and instead I focused on maintaining my life as best as I could. There seemed to be no help, no relief, no end in sight against this affliction. I was on a slow downward spiral that I knew would end my life.

One night as it came to head, one friend pleaded with me to at least try MDMA-assisted therapy. I agreed. I was accepted into the MDMA drug trial whose data you're reviewing today, and I admit that I did not have a lot of optimism as I drove to Boston to attend my intake sessions. What I found is there was a psychiatrist and a therapist who are incredibly knowledgeable in PTSD, its cause and its effects, and its treatments. They were

completely compassionate and truly believe that I could be helped.

Although my first time, I ended up being on placebo. I was told that I'd be included in the crossover trial, and I cannot put into words how much this drug-assisted therapy helped me when I got into it. The parts of me that were permanently damaged, the way I saw the world and I responded to stimuluses, it changed. Innocuous sounds and actions that you guys would not notice, that used to fill me with rage, anger, fear, anxiety, and shame, they now go by so unnoticed that I feel normal.

I count myself incredibly lucky to have been through this treatment and exceptionally optimistic for what I could do to help others like me, and as you consider your decision today, I would ask that you remember my story. This treatment has the potential to help in saving so many lives, as I know that it saved mine. Thank you for your service, and thank you for giving me some time to speak.

DR. NARENDRAN: Thank you.

Speaker number 5, please unmute your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and organization for the record. You have three minutes.

MS. DEVENOT: My name is Nese Devenot, and I'm a researcher at Johns Hopkins University with expertise in psychedelic bioethics. I co-authored the Citizen petition to extend the open public hearing at this meeting.

Lykos claims its training program will reduce the risk of boundary violations by teaching the specific psychological intervention from its clinical trials, but the clinical trials failed in this regard. This committee has been misled by Lykos to believe that this intervention was non-directive and empathetic.

Lykos has obscured its actual intervention and its submissions to the FDA. This intervention is acknowledged in this 2015 paper by founder Rick Doblin. Doblin admits that Lykos' entire therapeutic approach is based on Stanislav Grof's

spiritual teachings and that the essence of that treatment approach is a death-rebirth process. Although this specific intervention isn't in any of the briefing documents that were submitted to the committee, it is associated with identifiable patterns of harm across Lykos' clinical trials.

Lykos' intervention is described more fully in the book, Integral Psychedelic Therapy. Two of its three editors were Lykos trainers and phase 3 therapists, and it was endorsed by prominent members of Lykos' inner circle. In this book, Veronika Gold, a Lykos supervisor, trainer, and phase 3 therapist, describes pinning down a patient as their distress escalated to the point of shouting, quote, "Go away. Get your effing hands away from me," end quote, but Gold did not stop. As demonstrated by the many Lykos therapists who endorse this abusive practice, this is an accepted component of the intervention that Lykos presented to this committee as necessary for positive patient outcomes.

Lykos would like this committee to believe

that significant boundary violations were limited to a single phase 2 participant. Although this participant enlisted the media to draw attention to the dangers of Lykos' therapy, the components of her on-camera physical assault are still explicitly taught as part of Lykos' intervention.

After submitting my 17-page written comments to this committee, I was connected with a phase 3 participant whose PTSD symptoms were exacerbated by Lykos' clinical trial. I learned they were under the care of therapist Veronika Gold, and they continue to experience flashback nightmares of the specific intervention that Lykos expects this committee to support.

Lykos argues that its training will ensure that boundaries are maintained, but its intervention heightens risks for participants by incentivizing boundary violations. In addition to gross violations in phase 2, previously unreported violations include Lykos' senior leadership having sexual encounters with a vulnerable individual who was then recruited into phase 3. The most

significant harms in Lykos' clinical trials were not caused by MDMA, but by the people who were entrusted to supervise this administration. If the committee would like additional information, I'm happy to provide it. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 6, please state your name and introduce yourself. Please state your name and organization for the record. You have three minutes.

DR. ABRAMS: Thank you. Good afternoon. I'm Dr. Michael Abrams from Public Citizen's Health Research Group, and I have no financial conflicts of interest on this matter. The committee today is mainly evaluating the treatment-associated experiences of about 170 participants who took part in the placebo-controlled efficacy studies, and about 470 individuals whose data were used to consider midomafetamine as a psychotherapy enabling treatment for PTSD.

The two pivotal randomized clinical trials were functionally unblinded, and thus likely biased

towards favorable drug effects. Patients and therapists likely knew who received the drug, and anecdotes suggest some therapists abused that knowledge to manipulate patient beliefs.

Despite reluctantly green-lighting these trials, the FDA's briefing materials for this meeting said this, quote:

"The contribution of the likely expectation bias cannot be discounted, while it also cannot be quantified. For the primary outcome in both trials, statistical estimates of a 9-point difference in one trial, a 12-point difference in the other, favoring the drug treatment did not or only barely achieved the 10-point difference the FDA agreed represents the low end of meaningful improvement in PTSD related symptoms.

"Moreover, the pivotal trials were confounded by the inclusion of imprecisely defined multi-hour psychotherapy sessions." To quote the FDA briefing materials another time, quote, "The contribution of psychotherapeutic support sessions to the overall efficacy results cannot be fully

quantified or understood," close quote.

Even as the results show that both the drug and the placebo-exposed patients improved markedly, though variably, adverse events that were markedly more prevalent with the drug treatment compared to placebo included blurry vision, gastrointestinal disturbances, thermal regulation disturbances, acute blood pressure increases, headache, dizziness, tremor, psychiatric symptoms such as insomnia, and of course, the abuse and dependence potential of the treatment are well established in human and animal studies.

Thus, as the FDA briefing materials state, it is particularly concerning that, quote, "the applicant did not appropriately document central nervous system-related adverse events," closed quote, as advised by the agency's control substance staff. Based on the available evidence and considering the main deficiencies of this drug application, the known benefits of midomafetamine to treat post traumatic stress disorder, those benefits are insufficient to outweigh the many

risks. Thus, Public Citizen's Health Research Group urges this committee to vote no on the voting questions before you and to recommend to the FDA that MDMA not be approved. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 7, please introduce yourself. Please state your name and organization for the record. Go ahead.

DR. ALPERT: Hello. My name is Dr. Jonathan Alpert. I'm Chair of the Council on Research for the American Psychiatric Association, and I have no conflicts of interest. With over 6 to 7 percent of the American population affected during our lifetimes with PTSD, the APA recognizes the major need for effective, accessible treatments for PTSD.

PTSD has a pervasive impact on multiple domains of functioning, and is often a chronic condition with widespread impairment and suffering and high rates of comorbidity, including depression, substance use, cardiovascular, pulmonary, neurological disorders, and an elevated risk of premature death from suicide and other

causes. In addition, PTSD has a disproportionate burden on vulnerable and minoritized populations, as well as on women and veterans.

We have two reasonably effective FDA-approved pharmacotherapies for PTSD, but there are high rates of non-remission. About 70 to 80 percent of people failed to remit, and there have been no new approved treatments by the FDA, pharmacological treatments, of over more than two decades. We have a growing range of evidence-based trauma-focused therapies, including cognitive behavior therapies, exposure-based therapies, eye movement desensitization, and reprocessing therapies, and others; however, many people in the United States don't have access to the expertise needed to provide that care, and there are also high rates of dropout from those therapies.

MDMA represents a promising treatment for a devastating illness; however, there are significant limitations to the current evidence-based on MDMA for PTSD. There are high expectancy biases and functional unblinding of participants, and we

assume also unblinding of therapists, although to our knowledge, that was not assessed. Nearly half of the participants in the phase 3 trials had had prior exposure to MDMA, which is unusual for drug treatment studies. That means that people who presumably had positive or neutral effects from MDMA in the past might be more likely to have participated, and those who had distinctly negative experiences were less likely. That's a threat to the generalizability of the studies.

In addition, the phase 3 studies used a novel time-intensive psychotherapy involving approximately 84 hours of therapist time. It's unclear how scalable that will be in real-world clinical settings. It's also unclear, based on the study design, the contribution of those psychotherapies to the drug effects that were observed, and finally, there's limited long-term data on safety and relapse rates beyond two months.

So, in conclusion, the APA supports research and therapeutic discovery into psychedelic agents that's pursued with the same scientific integrity,

rigor, and regulatory standards applied to other promising therapies and medicine. PTSD is a disabling, potentially life-threatening condition disproportionately affecting vulnerable populations. The treatments for PTSD must occur in clinical settings in which comprehensive consent, experts, psychiatric evaluation, treatment, monitoring, and follow-up care are all assured.

Future research needs to include head-to-head comparisons with other FDA-approved medications and evidence-based PTSD psychotherapies; safety and efficacy of co-administration of MDMA with other psychiatric medications that were excluded in the phase 3 trials but may be necessary in real-world clinical populations; safety and efficacy in adolescent populations with PTSD; further evaluation in diverse real-world --

DR. NARENDRAN: Dr. Alpert, you have to wrap it up.

DR. ALPERT: -- community settings; and preventative steps that avoid conflation of

approved medical use and use outside of a clinical framework; and finally, ensuring equitable access, if MDMA is approved for PTSD, so people who most need it are not left standing last in line. Thank you so much.

DR. NARENDRAN: Thank you.

Speaker number 8, begin and introduce yourself. Please state your name and organization for the record. You have three minutes.

MS. HARVEY: Hello. My name is Ifetayo Harvey. I'm the Executive Director of the People of Color Psychedelic Collective. My organization provides education and community outreach to those interested in learning about psychedelics and ending the war on drugs. I've worked in the broader drug policy reform field for 11 years. In those 11 years, I worked as Rick Doblin's assistant at the Multidisciplinary Association for Psychedelic Studies for eight months in 2015. Despite my poor treatment as an employee, I'm grateful to MAPS for pioneering a movement around psychedelic healing in clinical settings.

I believe part of the reason why we're here is the question surrounding the efficacy of MDMA-assisted psychotherapy for people with PTSD, but I also think the other part of the reason why we're here is because this is the first time, in my opinion, that advocates have had the space to share and have others engage their concerns. There's a tendency in the psychedelic community to shy away from critiques or confrontations. This hearing may not have been as bustling had leaders in the field addressed some of the questions speakers are bringing up today.

I consider a lot of the speakers colleagues, and one common theme between us is that we entered the psychedelic field as enthusiasts for the movement, yet we know when we love something, you must critique it. For the last few years, I've critiqued MAPS for their lack of inclusion of non-white study subjects. I've also witnessed the field, and MAPS dismissed valid concerns from other critics and a refusal to engage those concerns.

While some may see this hearing as a

detraction, I see it as an opportunity to improve our movement and ensure consumer safety. After seeing the evidence of abuses across boundaries and buried discrepancies, I've concluded that there needs to be more rigorous research on MDMA-assisted psychotherapy before it's brought to the public. As an advocate for ending the war on drugs, I believe that all drugs should be decriminalized and regulated, yet there's a need for research-backed understanding and guidance on safe, effective use of psychedelics. Rigorous accountability standards and a moral degree of integrity are central to my commitment. I hope that after this hearing, the field starts to hold itself to a higher standard.

DR. NARENDRAN: Thank you.

Speaker number 9, please state your name for the record. You have three minutes.

MS. GREENSTEIN Hi. My name is Kayla Greenstein. I'm a psychology PhD candidate at the University of Sydney, and I used to work in sexual assault response. I have no financial disclosures.

It's 4 am in Australia, and I would rather

not be awake right now, but I am deeply concerned about the Lykos model of MDMA-assisted therapy. When I started my PhD two and a half years ago, I wanted to conduct a psychedelic clinical trial for PTSD, but as I looked at the psychotherapy component, I quickly realized there were very serious issues. My research now focuses on the theoretical underpinnings and use of touch in psychedelic therapies.

I have read the Lykos therapeutic manual very closely, and I've read all of the references cited in the manual. The core idea of the therapy is that we all have an inner healing intelligence that can be accessed through MDMA and other non-ordinary states of consciousness. Given the centrality of the inner healing intelligence in their therapy manual and as a proposed mechanism of action, I'm really surprised we didn't hear more about it today from the sponsor.

It was also really concerning to hear the sponsor say that MDMA-assisted therapy facilitates memory recollection. This is a highly

controversial idea that sits alongside the idea that MDMA elicits a more authentic version of the self connecting to the inner healer and archetypes in the collective unconscious. Using touch and body work to clear energy blocks in patients are also in the therapeutic manual.

Much of the backing of the manual is based in New Age psychospiritual theory. It is Rick Doblin's goal to have a global spiritualized society by 2070. Controversial New Age psychiatrist, Stan Grof, comes up 14 times in the therapy manual. He believes all psychopathology is rooted in traumas in the birth canal. Here's his book and some of those diagrams. This includes homosexuality, which Grof believes is a dysfunction that comes from trauma in stage 3 of the birth process. Grof's work is homophobic and misogynistic. This is not a safe therapy model. These theories were an integral part of the phase 2 trial abuse, and we need a different therapeutic manual with contemporary co-designed research supporting it.

I also recently published on the lack of mention of discussion of coercive control in MDMA couples therapy where one person has PTSD. In response, MAPS affiliated researchers attempted to have my work removed with faceless accusations. After a lengthy process, I demonstrated my critiques of their work were entirely accurate. There has been no recognition of the role of coercive control and increased vulnerability within couples and families in the treatment process.

I am still hopeful about MDMA-assisted therapy, and I greatly look forward to seeing the research coming from labs that are not associated with MAPS and Lykos. I wish I could support this application; however, I believe approving this model of MDMA-assisted therapy would result in substantial further harms. I very much hope that if it is approved, I'm proven wrong about that. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 10, please introduce yourself. Please state your name and organization

for the record. You have three minutes.

MR. WATERS: Thank you for the opportunity to speak today. My name is Brett Waters, and I'm an attorney and the Co-Founder and Executive Director of Reason for Hope, and Co-Founder of the Veteran Mental Health Leadership Coalition. Reason for Hope is named in memory of my mom, Sherrie Hope Waters, who I lost to suicide in 2018. I lost my grandfather, her father, to suicide when I was young. He was a World War II veteran who was shot down in the South Pacific at the age of 16.

Reading the suicide notes my mom left behind -- which she wrote over the course of several years, she was struggling until her final note -- serve as a visceral reminder of why I got involved in this advocacy and with the limitations of currently available treatments for trauma-related conditions such as PTSD and many others.

My mom's struggles began in early childhood from trauma long before the suicide of her father. She never spoke about it. I had to learn from the

notes she left behind. While she made an attempt at therapy over the years, it can be incredibly daunting to even begin confronting such challenging content and exhausting to continue even if you can manage to start, and it only becomes harder and more exhausting to seek help over time, particularly for someone experiencing extreme depression and brain fog.

I never fully understood my mom's aversion to antidepressants until I was prescribed them myself after struggling to return to work following her suicide. Unsurprisingly, these did not help resolve the underlying feelings of pain, grief, and guilt. While they had a brief mild effect that helped me get back to work, between the emotional blunting and other side effects, they were ultimately counter-productive and made the idea of going to therapy and processing more difficult. The longer I took them, the worse it got until I made the decision to stop after five years, which required multiple failed attempts and experiencing further withdrawal effects.

My experience and that of my mom and grandfather are, unfortunately, all too common. There are so many people suffering rates of PTSD, depression, suicide, increasing for decades, yet we've seen little progress in new treatments despite the clear limitations of what's currently available with psychotherapy and SSRIs. I appreciate the thoughtful questions the committee has asked in evaluating this very challenging and novel application; however, I urge that you not lose the forest for the trees.

MDMA-assisted therapy offers a seemingly obvious and logical approach to PTSD treatment, as the drug's ability to rapidly establish therapeutic rapport and reduce fear response makes it easier to commit to and engage in a psychotherapeutic process that involves confronting often highly traumatic memories. A truly novel treatment of this sort is desperately needed for many long-struggling individuals. There are ample patients who will be eager to move away from the need for chronic daily medication for a more holistic, robust, and

seemingly durable approach to healing, which will extend well beyond those with diagnosed PTSD.

As someone who has also struggled with an eating disorder, adult restricted food intake disorder for my entire life, for which there are no approved treatments and for which SSRIs are therapy help, I expect this will probably be my best option in the near future.

While we believe MDMA-assisted therapy is clearly efficacious, any treatment that can produce such benefits can also cause harm, and we've seen and heard here about the risk of abuse of vulnerable patients. We believe the committee and FDA could further mitigate risks through requiring remote live video monitoring and a default requirement that all psychedelic administration sessions be video recorded unless explicitly objected to by a patient in writing.

Nonetheless, given the FDA's already very stringent proposed REMS --

DR. NARENDRAN: Speaker number 10, you're going to have to wrap up.

MR. WATERS: -- including patient enrollment --

DR. NARENDRAN: You're almost out of time.

MR. WATERS: -- we believe the benefits of MDMA-assisted therapy clearly outweigh the risks, which is the primary issue that you are here to consider. Thank you again, and please use this opportunity to save lives. There are too many people who have been struggling for far too long. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 11, please state your name for the record. You have three minutes.

DR. PACE: My name is Brian Pace. I am a lecturer teaching psychedelic studies in the Department of Plant Pathology at The Ohio State University. I am also a co-author of the Citizen petition, which raised serious concerns about the NDA under review. I thank the FDA for granting extended time in this response to our petition. No conflicts.

I submit that Lykos is a therapy cult that

uses the application under review to further mystical and utopian goals. This lens explains the mounting allegations against them regarding research misconduct and clinical trial participant harms. In my paper, Right-Wing Psychedelia, I analyze Lykos' leadership's simply-stated aims for instrumentalizing the drug under review to change people's beliefs as part of an ongoing project of global spiritual conversion. This spiritual conversion underlies their promise of solutions to more material concerns like bringing about world peace or solving climate change.

While these are not the first dubious promises to be made by applicants before this agency, they are perhaps the most grandiose. I'm obligated to state the obvious. MDMA-assisted therapy for PTSD is not going to result in the, quote, "spiritualization of humanity," unquote, and such claims are the prophecies of a therapy cult.

The FDA is under no obligation to evaluate these spiritual claims, but this agency is tasked with monitoring institutional review board

compliance, and act when study sponsors confessed to casual human experimentation with the drug under consideration at Burning Man. That Lykos leadership felt comfortable admitting this while clinical trials were ongoing betrays a lack of internal accountability and an organizational culture of deep impunity. Lykos has exploited this lack of monitoring and sanction from the FDA; in fact, they're betting on it.

At South by Southwest this year, Lykos' CEO, Amy Emerson, shared that patients presenting increased suicidal ideation is, quote, "Actually part of the process," unquote, of psychedelic therapy. In the same breath, she acknowledged that committing instances like these to medical records would be poorly received by gatekeepers of public health. Omission of adverse events is one of the specific allegations leveled against the applicant.

As I mentioned in my written comment, an organization convinced it's on a mission to save the world might find justification of any means to do so, but the FDA's broadest mission is that of

protecting public health. Patients living with PTSD need rigorously tested care, not the faith healing of a therapy cult's latest rebrand of laying on of hands.

The concerns I share today aren't about the safety of MDMA, but rather the people who have been administering and supervising this medicine. Harms and misconduct will scale if they are allowed to train and certify therapists. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 12, please state your name and organization for the record. You have three minutes.

PASTOR WELKER: My name is Joe Welker. I'm the Pastor of East Craftsbury Presbyterian Church in Craftsbury, Vermont. I have no financial relationships to report. I completed chaplaincy training at the Charles Georgia VA Medical Center, where I worked with many veterans who suffered from PTSD. I know that condition is not trivial.

I fully support, and I'm grateful for anyone who's got and will get healing from MDMA for PTSD,

including in this trial, but I also speak as a former member of the psychedelic industry before I became a whistleblower on a study at Johns Hopkins University, where funders and researchers with intimate ties to Lykos, then known as MAPS, advanced the religious and spiritual agenda that is shared by Lykos founder and executive director, Dr. Rick Doblin, and as Dr. Pace has just described.

I feel compelled to echo concerns warning the public of what is an openly known secret in this psychedelic industry, that in the words of Dr. Doblin, his long-term desire is, quote, "spiritualized humanity," politically advancing this mission using the representation of science. This study has functioned as that first politically savvy Trojan horse of that mission.

As I submitted in written comments, while one may argue the legitimacy of psychedelic spiritual beliefs on their own merits, how do we trust data when a company not only has financial conflicts of interest, but open spiritual and

religious conflicts of interest? And like the worst of religions, including my own, what happens when people are abused in the name of a religious mission? As we saw in these trials, they are often discarded, silenced, minimized for political gain, and tossed away as inconvenient.

So while I support anyone who gets healing from MDMA therapy, I'm here in support of people harmed in these trials: many other victims of psychedelic therapy abuse; all of their family and friends; former Lykos employees; academics; whistleblowers; the many who have spoken anonymously to the media; journalists; and others who have concerns about the intermingling of a utopian spiritual movement with science.

I must also say there is a certain irony in questions earlier about risk assessment and whether participants increase an illicit use of MDMA. Both the FDA and the public should be aware that this study is run primarily by people with an extensive use of MDMA in illicit settings. It would be hard to find a bigger promoter of illicit MDMA use in

American history than Dr. Doblin. Dr. Doblin's public advocacy gives the impression that Lykos leadership would think any increase in illicit use would not be a bug, but a feature.

Again, I am a former psychonaut, and I do fully support people who got healing in this trial or elsewhere from psychedelics, and I support continuing research into MDMA therapy. But while Lykos leadership may envision a spiritualized humanity, in this very study, Lykos treated the people who were harmed under their care with a falsely spiritual inhumanity. Regardless of the decision made today, and in August, the public deserves to know that. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 13, please introduce yourself. You have three minutes.

MR. WITKA: Hello. My name is Beau Witka. I just want to start off by saying it was very hard for me to join you today, and it was equally challenging for me to write the statement that I'm reading since I currently find myself in the midst

of what I openly describe as the most terrifying time of my life.

The frightening state I'm in, and I've learned to cope with to the best of my ability, began immediately following a single-guided MDMA-assisted therapy session on February 19, 2023. In spite of my difficulties and discomfort presenting to you, I want to be as candid as possible about my experience since I'm living proof of the dangers of the therapy component of MDMA-assisted therapy, and I feel like I have a duty to educate and warn others about something I was completely ignorant of prior to my treatment last year, that MDMA can cause lasting harm to a client when administered under the guidance of an inept and/or inexperienced therapist.

I'm determined to continue to share my story publicly so as to not allow what happened to me happen to others. I have nothing against MDMA and, in fact, I know from personal experience that this drug has tremendous clinical potential for positive outcomes when administered correctly.

In late 2022, I participated in a group journey where I was not working with a therapist. This experience was extremely positive and changed my life in ways that years of talk therapy could not. The MDMA that I consumed with this group came from the same source as the MDMA I was given on February 19, 2023, which proves how impactful the role of a therapist can be.

Speaking of therapists, it's important for me to note that the licensed therapist who guided me is a graduate of the California Institute of Integral Studies, Center for Psychedelic Therapies and Research, which trains therapists for MAPS clinical trials. She has a doctorate, many years of experience, various certificates, and claims to specialize in treating trauma.

This experience has completely derailed my life. I've been unable to work for the last 15 months, and I've had to live with a family member while I attempt to recover on my own. Just a few of the symptoms I've experienced on a daily basis with often abrupt, inconsistent, and

unpredictable fluctuations include extreme exhaustion; brain fog; severe cognitive impairment; unrefreshing sleep; headaches; eye issues; and a long list that's too extensive to share with you today.

I'm a hundred percent pro MDMA and would like to see the drug legalized for therapeutic use; however, I cannot support MDMA-assisted therapy being allowed to go mainstream until more training and research is conducted to better understand how to avoid outcomes like mine, and more importantly, how to support people who experience extended difficulties. There is zero support for people like me and absolutely no safety net in place.

I want to end by saying, two years ago this topic and meeting would have meant very little to me, but since February 19th of 2023, it has become an extremely personal subject, and thank you again for holding this hearing.

DR. NARENDRAN: Thank you.

Speaker number 14, please introduce yourself. You have three minutes.

MS. YOUNG: Hello. My name is Deran Young, and I'm speaking on behalf of Black Therapists Rock and the Veterans Mental Health Leadership Coalition. I am a mom, a licensed therapist, a retired military mental health officer, and the Executive Director of Black Therapists Rock. Black Therapists Rock is a non-profit organization that mobilizes over 30,000 BIPOC mental health professionals to reduce intergenerational trauma in marginalized communities.

When I personally left my hometown of Wichita Falls, Texas to join the Air Force shortly after high school, I had no idea what the word "trauma" really meant. I had witnessed and lived it throughout my childhood, but didn't have the language to articulate the pain in my heart that I carried for many years. I grew up in a town that was deeply segregated by race and class and in a town that regularly held KKK rallies.

In addition, I was the oldest of three girls whose mother attempted to numb her untreated symptoms of bipolar disorder with crack cocaine

throughout the '80s and '90s. As a child, my family heavily relied upon government assistance for medical care, food, and housing, but I was specifically taught to not trust these agencies and was repeatedly told that what happens in this house stays in this house.

While I was an active duty captain stationed at Aviano Air Force Base in Italy, I provided mental health treatment directly to military members, and families as well. During that time, I established Black Therapists Rock shortly after the murder of Trayvon Martin to work on my own personal healing. By the time I had gained an undergrad in social psychology and two master's degrees, however, the intellect in my head did very little to heal the traumatic experiences that still lived in my body.

During my own MDMA therapy session, I came face to face with my own racial trauma and was able to acknowledge the multi-layered fear of men, white-body people, and all authority figures. My healing from this session was so profound that I

decided to get trained in MDMA therapy myself. I also advocated and facilitated scholarships to train over a hundred therapists of color in psychedelic assistance therapy specifically for racial trauma to ensure that there will be enough culturally attuned professionals if and when this medicine is approved as a treatment for PTSD.

Racial trauma, deeply ingrained through generations of discrimination and systemic injustice, leaves scars not just on individuals, but on entire families and communities as well. The shame, fear, and deep mistrust it inflicts can be pervasive and debilitating. Traditional therapy approaches often fall short in addressing the depth and complexities of these types of traumas.

As my colleague, Nydia Guity, describes, "traditional talk therapy is like riding a bicycle towards healing, compared to psychedelic-assisted therapy, which is like riding a motorcycle." In terms of racial trauma, MDMA-assisted therapies offers a significant beacon of hope. Thank you for the time and allowing me to speak today.

DR. NARENDRAN: Thank you.

Speaker number 15, please introduce yourself. You have three minutes.

MS. MATHIS: Good afternoon. I am Naomi Mathis, Assistant National Legislative Director for DAV, Disabled American Veterans, an organization representing more than 1 million wartime service disabled veterans, and thank you for allowing us the opportunity to weigh in on this vital topic.

Post-traumatic stress disorder is among the signature wounds of war. PTSD touches the lives of veterans from every era, but the VA estimates nearly 30 percent of veterans who served in Iraq and Afghanistan will experience PTSD at some point in their lives. I am one of those combat veterans.

I can also tell you from personal experience that for those who live with PTSD, daily tasks that many take for granted seem insurmountable. Recurring nightmares and intrusive thoughts can make sleeping nearly impossible. Trouble with concentration or memory can make finding and maintaining work challenging. Suicidal and

homicidal ideations are causing us to lose more veterans by suicide than in the last 20 years of war. I could go on and on about the examples of the reality many veterans face daily, but we're here to talk about possible solutions.

We know that current treatments remain woefully deficient for far too many veterans. Many anecdotal and peer-reviewed evidence show high dropout rates of currently available treatment options, and the last breakthroughs in PTSD medication are now decades old. With VA's most recent annual suicide report, we know that veteran suicide is on the rise. We should consider every tool in our arsenal in lowering and one day eliminating this epidemic.

DAV believes that every veteran deserves the best world-class care available. Simply put, we need innovation. The preliminary data on MDMA-assisted psychotherapy appears promising. While DAV does not take a stance on the state of the science, we are heartened to see such research take place. The VA announced its funding of

research on MDMA's effects on treating PTSD and psilocybin for depression, and DAV looks forward to their results, but in the meantime, we support making any FDA-approved treatments and protocols available through the Department of Veterans Affairs.

VA has the highest standards when it involves research and has expertise in studying the veteran population ethically. As the FDA considers this novel treatment, we cannot forget that veterans' trauma took place on our nation's watch and would not have occurred were it not for their military service. There's an old adage, "You break it, you buy it," and while no veteran is broken, some of us may return slightly bent. As such, our nation and federal government have a solemn duty to turn over every stone to find better more effective treatments. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 16, please introduce yourself. You have three minutes.

MR. LUBECKY: My name is Jonathan Lubecky.

As far as financial, I used to have a consultant contract with MAPS from April of 2018 until about a year and a half ago. I've never been compensated by Lykos Therapeutics.

I deployed to Iraq with Bravo Battery 5th and 113th in 2005. When I came home, I suffered with PTSD. For eight years after I returned from war, my existence was plagued by nightmares, crippling anxiety, depression, and persistent suicidal ideation. I was prescribed antidepressants and countless other meds. I underwent a lot of therapy and treatments. None worked. I lost hope, I was hospitalized, and attempted to take my life several times.

I'm here today because unlike the 76,538 veterans who have taken their lives since I underwent my first session of MDMA therapy in 2014, I participated in a Lykos Therapeutics clinical trial, and for the past decade, I have been allowed to live, to truly live. Since MDMA therapy healed me 10 years ago, I have endured and healthily navigated many traumatic experiences. I've had two

people die in my arms I tried to save. I lost both my parents and many friends. My beloved service dog Becky died in my arms. I helped my son deal with his own PTSD after he almost died on a cruise ship and was evacuated by the Coast Guard.

But my ultimate test of the long-term efficacy of MDMA therapy came in December of '22 when I chose to travel to Ukraine to provide humanitarian aid and medical support to civilians and military fighting the Russians on the front lines. I was frequently exposed to missile and drone strikes in Kiev, and I was close to gunfights and artillery in the Donbas. It was worse than anything I saw in Iraq; yet none of these experiences triggered the PTSD I once suffered so horribly with. I remain happy and healthy today.

If the FDA approves MDMA, my hope is that the therapy will quickly be covered with by health insurance, Medicare, Medicaid, and VA. That would mean that 80 percent of the country could access this groundbreaking, highly effective therapy and be allowed the opportunity to heal in a safe,

therapeutic environment. Yesterday, I wandered among the marble tombstones of Arlington, visiting friends; some lost to age, accidents, combat, and a lot to suicide. One of those markers should have my name on it.

I'm testifying today because I want all my brothers and sisters, all human beings, to be allowed the same chance to heal that I was given. I've given hundreds of interviews sharing the most personal and intimate parts of my life. I've done so to provide hope to those who suffer as I once did. I'm here fighting for the lives of the 171 men I deployed with. That number is now down to 166, and we buried another one in January.

Two weeks ago, a friend who lost his leg in a roadside bomb called me, begging to try the therapy that saved me. I've lost count of all the people who have reached out to me to say, "I was going to kill myself, but I saw you, so I'm going to wait." For a decade, I've had to tell hundreds of people who have reached out that help is coming, but we have to wait for the proper approval

process. That simple ray of hope has saved so many lives, but I fear what will happen to them if this therapy is not approved.

Last year, 50,000 Americans committed suicide, another annual increase. Imagine how many lives your vote could save. Imagine how many will be lost if you vote against this vital therapy. The VA can and has safely and effectively administered MDMA therapy. Today, you will vote on whether my friends live or die. I pray you will vote to save them. And for those who doubt whether I've been healed, rather than condemning veterans to suicide, come with me. There's an empty seat on the ride to the front lines. We can feed people. They need it. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 17, please introduce yourself. You have three minutes.

MS. SAYANI: Hi. My name is Sehrish Sayani, and I have no affiliation with any organizations. I was a participant in this trial over the course of two years. I received the placebo treatment in

2022, being offered to come back in 2023 for the MDMA-assisted therapy. I am the definition of this experiment, having done both holistically with and without the assistance of the medicine. I can wholeheartedly say that I am a different, better, stronger, and more courageous version of myself due to this groundbreaking therapy.

When I signed up for this trial, I had accepted my PTSD diagnosis as something I would live with forever. It affected every aspect of my life, but I had learned to manage my symptoms such as severe anxiety, panic, insomnia, and hypervigilance, to name a few. I couldn't imagine a world where there was a solution. Now, I get to fully live my life. My perspective on the world has changed because my perspective of my experience changed.

Many trauma survivors fight reality and acceptance because they had no control over their experience. I learned that I was living in survival mode, and once I was able to process my grief and trauma, I felt self-empathy and self-love

for the first time in decades. My trust in this world grew again. I started looking at the glass half full instead of being stuck in this endless victim narrative I had so long held in my head.

The two trials were vastly different. The placebo sessions didn't quite stick like the MDMA sessions did. It's tough to put into words over a few minutes, but the best way to describe it is I found my place and purpose in this world. I connected to my mind, body, and soul in a way that restored my faith again.

Psychedelics are often misunderstood as a magic pill. In reality, the medicine is a vehicle, yes, but the patient is doing the work. It was not an easy process by any means, but I and every participant in these trials put in the work to get the results for the data that you see. Although my score saw massive improvement, what the data can't show you is that the MDMA sessions didn't magically get rid of my trauma. That's not why my numbers changed. It's because I did the work, with the help of the medicine to create space and capacity

within myself to hold my experience.

I got my power back. People used to always tell me I was strong, but I never felt like it. Now, I feel that I embody that strength. I practice gratitude for my life every day and remain in the present rather than thinking about the past or worrying about the future. I feel peace, calm, and safety after being robbed of it for so long. These are basic human rights everyone deserves that struggles with PTSD, and we are at the doorstep with MDMA-assisted therapy as a solution for those who need it. Thank you for the opportunity to speak today.

DR. NARENDRAN: Thank you.

Speaker number 18, please introduce yourself. You have three minutes.

MR. DARAEIZADEH: Hello. My name is Pedram Daraeizadeh, and I have no conflict of interest. Please note, my speech may be triggering for some.

It's a chilly fall morning in 2018. I'm at home with our 2-year-old daughter. My wife brings breakfast, but the coffee is not to my liking. An

innocent mistake triggers an intense memory, once again pulling me into the past. Suddenly, a surge of anger strikes like lightning. My heart races, my skin sweats, my entire body burns. Cutting another rage attack, I lash out at my wife for ruining the coffee. Making matters worse, I throw the breakfast plate across the room. It shatters. Our daughter cries, and my panicked wife grabs her and fleas the house.

That day hope faded, but it was also the day I discovered immunotherapy for PTSD. I was tired of triggers, flashbacks, nightmares, isolation, depression, feeling unsafe and disconnected. To end my suffering, I was willing to end my life, unable to bear such overwhelming pain. A childhood scarred by revolution, war, and oppression, followed by an early adulthood, traumatized with trafficking, assaults, and death threats had left me with severe PTSD.

In early 2019, I participated in a phase 2 study of MDMA therapy. While it didn't cure all my symptoms, it served as a catalyst that truly

transformed my life. It empowered me to face my trauma safely, accelerate my healing, reopen my heart, and rediscover trust and self-love. Today, I stand here not to inflate hype or inhibit hope, but to offer a nuanced perspective. Assessing the benefit-risk profile of this treatment extends beyond expertise, data, and opinions. It needs integrating diverse viewpoints from participants, especially underserved communities with firsthand experience.

The mind-altering effects of MDMA require deep respect for autonomy. Patient safety mandates highly trained ethical therapies with a strict oversight. As the impact unfolds gradually, proper aftercare becomes crucial. Without it, patients remain at risk, and their treatment potential wanes. Healing starts with therapy, not mere medication. MDMA enhances therapy, yet regulators only evaluate the drug. Prioritizing psychological safety alongside drug safety is vital. Strong regulatory support can prevent systemic issues and unintended harm.

Current clinical trial frameworks may not suit psychotic research. Perhaps it's time to update our scientific gold standards. MDMA therapy, like any treatment, carries risks, but so does leaving patients without options. Existing treatments aren't helping, causing unwanted dependency and side effects.

To conclude, in mental health, we need momentum, not miracles, as individual trauma and healing significantly affect public health. Five years post-treatment, my healing journey continues. I leave work and nurture relationships with renewed mindset and meaning. This treatment, merging the medical with the mystical, forever changed my relationship with suffering.

To improve care, we must unite key stakeholders, amplify lived experiences, train and supervise therapists rigorously, and provide comprehensive aftercare support, including for caregivers like my wife. MDMA therapy may not be a magic bullet to save the world, but thanks to the courage of participants, it could deliver powerful

results, potentially saving the lives of trauma survivors in desperate need. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 19, please introduce yourself. You have three minutes.

DR. AGRAWAL: Good afternoon. My name is Manish Agrawal, and I'm the Co-Founder and CEO of Sunstone Therapies, a mental health company dedicated to the research and delivery of psychedelic-assisted therapy. Prior to Sunstone, I was an oncologist for 20 years and treated thousands of patients. I also have decades of clinical research experience, including a fellowship and faculty position at the NIH.

I founded Sunstone because I saw the potential of psychedelic therapy to help cancer patients who were suffering as much emotionally as they were physically. Our clinical research has since expanded to include multiple populations and compounds, including MDMA-assisted therapy for individuals with chronic PTSD. Over the past year, I believe Sunstone has treated more patients with

non-ketamine, psychedelic-assisted therapies than any other medical site in the country.

Over 90 percent of the patients with PTSD in the Lykos-sponsored expanded access program for MDMA-assisted therapy have been enrolled at Sunstone. This gives us a unique perspective on the efficacy and impact of this treatment. As principal investigator, I have personally witnessed the transformation and healing that these patients experience. The therapists on my team, who have worked with PTSD patients their entire careers, say they have never seen such positive results in such a short time.

I want to tell you about one of those patients. We'll call her Lisa. Lisa is a 40-year-old mother of four children. She was suffering with PTSD caused by childhood violence and neglect. She had spent her entire life feeling disconnected and consumed by panic attacks and flashbacks. She received years of treatment in the form of traditional therapy, but found she was unable to unpack her densely-stored trauma.

Lisa had three MDMA sessions with the support of our therapist team. In her own words, Lisa shares that, "The MDMA treatment gave me an opening to retrieve and bring to awareness the parts of my life that would most support me, past and present. I saw not just the fears but also the strengths, and I was gifted back good memories as long lost pieces of myself resurfaced, the strengths I must have always had, because how else could I still be standing? Caring for my brain can become a privilege rather than a burden as I start my life again and find that I'm capable and ready."

This is just one positive story of many. MDMA is not a magic bullet and won't be suitable for everyone, but it will be life-changing for many people who have suffered for years, sometimes decades. I strongly advise that treatments be conducted in an appropriate medical setting with rigorous screening procedures and specialized therapist training. If this is done properly, given the evidence, I fully support the approval of MDMA-assisted therapy for PTSD. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 20, please introduce yourself. You have three minutes.

MR. SISKO: Distinguished members of the Psychopharmacologic Drugs Advisory Committee, thank you for your time and attention. My name is Sasha Sisko, and I have no financial relationships to disclose. Today, I will highlight four incidents of misconduct that raise significant ethical and legal concerns which merit your urgent consideration. I speak as a survivor of PTSD.

I will partially draw upon findings from my preprint entitled, Omission of Serious Adverse Events within MAPS-Sponsored Clinical Trial Publications. First, MAPS founder and Lykos Board Director, Richard Doblin, PhD, has described the publicly available footage of the physical sexual assault of a MAPS phase 2 trial subject in the treatment room as depicting a, quote, "technique" involving, quote, "psychodrama," that, quote, "can be beneficial in the context of psychotherapy," to which MAPS has published a book by Stan Grof

entitled, LSD Psychotherapy Which Endorses, quote, "sometimes inflicting pain," end quote, upon patients during, quote, "intense psychodynamic struggles."

Second, Dr. Doblin has proposed enrolling Ukrainians housed at refugee centers into a MAPS-sponsored clinical trial, examining MDMA-assisted group psychotherapy in sessions involving upwards of 100 participants. Although Doblin has described such, quote, "humanitarian projects" as, quote, "a risk that MAPS must take," his stated proposals violates the Nuremberg Code.

Third, I have documented dozens of instances of Dr. Doblin promoting off-label use of MDMA-assisted couples therapy, and furthermore encouraging the general population to practice MDMA psychotherapy as detailed in the MAPS treatment manual. Despite contacting the FDA and MAPS representatives about this, I have not, to my awareness, received a response to these matters.

Fourth, I have reported on footage depicting a MAPS trial subject informing multiple MAPS

researchers that they engaged in suicidal behavior during their clinical trial after their first MDMA treatment session; however, the relevant trial publication claims that no suicidal behavior occurred, quote, "during the treatment period after dosing." I can provide this footage to the FDA upon request.

It should be noted that Dr. Doblin famously criticized another psychedelic researcher for omitting a serious adverse event from their publications, stating that, quote, "There is no justification for this omission, no matter how unfairly the critics of this research may have used this information and no matter how minimal the negative persisting effects reported by the subject."

In conclusion, I urge the FDA and its Office of Criminal Investigations to thoroughly investigate these substantiated allegations to ensure compliance with federal laws and FDA regulations, while safeguarding the public's safety as well as the safety of patients. Thank you for

your attention. I yield my time.

DR. NARENDRAN: Thank you.

Speaker number 21, please state your name for the record. You have three minutes.

MR. GUARINO: Good afternoon. My name is Quaid Guarino. I have a master's degree in pharmacology from Georgetown University and have studied psychedelic drugs as part of my training. I have no conflicts of interest, and I support the approval of MDMA for PTSD.

MDMA is a psychedelic and stimulant drug that acts primarily in the central nervous system through multiple mechanisms, including releasing presynaptic 5-HT, dopamine, norepinephrine, inhibiting MAO A and B in elevating oxytocin levels. MDMA has been used as an adjunct to psychotherapy since the 1970s. Several limited clinical trials have demonstrated that MDMA-assisted psychotherapy can result in significant and sustained reductions in PTSD symptoms, and those trials have been adequately covered today.

It bears noting that MDMA without psychotherapy has not been tested, and the treatment should not be used without psychotherapy. Some concerns with the clinical trials include functional unblinding, the possible exclusion of patients with negative outcomes from long-term follow-up studies, and the lack of reporting of euphoria and other effects that might increase drug liking.

MDMA toxicity has been well documented; however, most reported adverse events have occurred in recreational users who are often taking doses of MDMA that are much higher than what is used in clinical trials. Serious adverse events with MDMA include cardiovascular events; hyperthermia; hyponatremia; myocardial infarctions; liver failure; rhabdomyolysis; and disseminated intravascular thrombosis.

Neurologic effects are also concerning. MDMA can induce cerebral edema, and by impairing GABAergic signaling in the brain can trigger seizures. Suicidal thoughts and ideation may occur

in patients taking MDMA. Although most clinical studies have reported no serious adverse events, this is not reassuring because most studies have been short term, and subjects in clinical trials may have been highly selected. Any evidence of unethical behavior or pressuring subjects not to report negative effects should be seriously investigated.

MDMA should be classified as a Schedule II drug. It has been claimed that MDMA does not have a high potential for addiction or abuse because tolerance develops rapidly and its most desirable effects diminish with the frequency of use; however, MDMA has already been demonstrated to have a high potential for abuse due to its popularity as a recreational drug worldwide. Although tolerance to MDMA could limit its abuse potential, it could also lead to dose escalation and its long-term, frequent or high-dose use that is most worrisome for neurologic and cardiovascular risk.

MDMA has been used historically as an unconventional adjunct to psychotherapy since 1970,

and recent clinical trials have demonstrated it to be an effective drug for PTSD, and it should be approved. Documented and potential harms dictate that if used cautiously and not as a first-line drug, that its use be restricted to people with severe PTSD who have failed other therapies and that its use be limited to qualified medical facilities.

We agree with the FDA on the necessity for a REMS, required phase 4 studies, and enhanced pharmacovigilance to assess harms, long-term effects, and drug-liking effects. We believe the currently available evidence supports the committee voting yes on both voting questions. An effective treatment alternative for PTSD should be welcomed, and with the appropriate precautions taken, it is time for MDMA to come out from the shadows. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 22, please introduce yourself. You have three minutes.

DR. BAGGOTT: I am Matthew Baggott. I am

the CEO of Tatogen, a company developing medicines that could compete with those of Lykos. From about 1999 to 2001, I worked as a part-time contractor for the non-profit former parent company of Lykos. I additionally advised Journey Clinical and the Noetic Fund.

I thank the agency, committee, sponsor, and other participants today for their work and for the opportunity to comment. I would also like to acknowledge and thank all those who've come forward to provide information and concerns about the NDA. I am speaking today in support of the approval of MDMA as a medicine. I speak as a neuroscientist who has conducted basic research on the pharmacology and toxicology of MDMA in humans and rodents. This has included administering MDMA to healthy volunteers and investigator-initiated studies. As a basic scientist, I focus my comments on risks.

Compared to most new chemical entities, the risks of MDMA are unusually well understood. To date, the National Institute on Drug Abuse has

funded $460 million of projects involving MDMA. Over 1500 participants have been given MDMA in studies not sponsored by Lykos. In addition to controlled experiments, 22 million people in the United States -- that's 7.8 percent of those 12 or older -- have reportedly used illicit MDMA preparations.

What we know from all this is reassuring. Despite often unsafe context, illicit MDMA use only rarely causes clinically meaningful problems. Controlled MDMA administration studies document manageable physiological risks such as time-limited cardiovascular changes and, when fluid intake is unrestricted, hyponatremia. Controlled MDMA administration studies also confirm acute self-report changes in mood and social feelings. These changes combined with MDMA's history raise reasonable concerns that MDMA might increase patient vulnerability to boundary violations or other harms.

Self-report measures appear to be our most sensitive way to track related potential

impairments. These measures indicate that acute emotional effects are diminishing by 150 minutes and are typically statistically insignificant by 6 hours after a single dose of MDMA in healthy participants. Additional data are needed to document the time course of changes in patients and/or when a divided dose is given.

As a separate area of concern, illicit MDMA preparations are reported by a subset of users to lower mood, beginning several days after exposure. Given this concern, I am reassured by the sponsor's and the agency's attention to suicidal ideation and behaviors as risks in patients. Overall, it is clear that MDMA can be used with acceptable safety under medical supervision. Additional data will help quantify likelihoods and time courses of specific risks in patients, but the balance of apparent benefits and risks appears to me favorable. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 23, please state your name for the record. You have three minutes.

MR. BROWNE: Thank you. My name is Nick Browne. I'm a 31-year-old veteran currently living in Denver, Colorado. My story starts back in 2010 when I was 18 years old, serving as an infantryman in the United States Army. Just four months after graduating basic training, I was deployed to Kandahar, Afghanistan with the 101st Airborne, where our primary mission was to help establish forward-operating bases within Taliban-held strongholds.

Our days were spent either actively engaging with the Taliban, defending patrol bases, and construction efforts of pushing deeper into the Taliban territory. I won't go into much detail about what we saw over there, but it was everything more entails, and then some. Little did I know that deployment was going to be the beginning of a decade-long struggle with addiction, anger, resentment, depression, anxiety, PTSD, and complete disconnection for myself.

I looked for help with the VA, where I was prescribed medications, and then prescribed

medications to help with the symptoms of other medications. Nothing ever really helped, and in some cases made things worse. I also tried other treatments like talk therapy, CBT, EMDR, even hypnosis, anything to get some help, and nothing really ever worked. Then in 2021, a decade after returning from Afghanistan, I stumbled on a MAPS study using MDMA-assisted therapy for PTSD and was fortunate enough to enroll and get accepted, ultimately changing my life forever.

The MDMA experience is difficult to describe, but it helped lift many of the mental barriers that stopped me from feeling or experiencing certain memories and emotions. It helped give me compassion for myself and allowed me to see my experience in Afghanistan in a new light, one that didn't blame me for being a bad guy that did horrible things. It helped ease my mind in public. It helped me get better sleep, have better relationships, and live what feels like a completely new life, along with a new perspective for my life and my place in it.

Now, I feel very blessed to have had the opportunity to have this experience when I did, but the reason that I am here today is because the battle isn't over. Many of my buddies are still struggling with PTSD. We're still losing thousands of veterans to suicide every year, we still have millions of Americans suffering from PTSD, and it's in my opinion that they need a valid treatment option; so please, I ask that you consider them as you make your decision regarding MDMA-assisted therapy as an option. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 24, please state your name for the record. You have three minutes.

(No response.)

DR. NARENDRAN: Speaker number 24?

(No response.)

DR. NARENDRAN: Okay. We will move forward to speaker number 25. Please state your name for the record. You have three minutes.

DR. SUTTON: Good afternoon. My name is Dr. Loree Sutton. I have no conflicts of interest

or relationships to report. During my nearly 30 years in uniform, I was privileged to serve as a Brigadier General and the United States Army's highest ranking psychiatrist. Career highlights include directing the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury and receiving the Bronze Star for actions in combat during Operation Desert Storm. Currently, I am working to bring more effective PTSD treatments to scale, leading to the topic of today's open public hearing.

Despite the best of intentions and billions of dollars over these last two decades, military and veteran suicides continue to increase far beyond pre-911 rates. Further, civilian suicides have increased by over one-third since the year 2000. Many of these suicides, civilian and military, are associated with PTSD. Developing better treatments is a pressing national imperative.

As we continue to face the pandemic-related aftermath, we must confront this trauma tsunami

head on. As U.S. Surgeon General Dr. Vivek Murthy recently stated, "Mental health is the defining crisis of our age. As a nation, we are in uncharted territory." Thus, the pending FDA decision concerning the new drug application for MDMA-assisted therapy for treating PTSD is the most timely, relevant, and transformational milestone.

Urgent change is needed. The current standards of care for PTSD have three things in common: limited symptom improvement, distressing reactions, and high dropout rates. As a result, veterans and their loved ones are increasingly seeking integrative non-drug and psychedelic treatments outside the VA system, even outside of the country. Their pioneering leadership and unflagging advocacy for advancing psychedelic therapies may be directly traced to the limitations of status quo treatments.

I first learned of MDMA-assisted therapy when reading about an Army sergeant who had recently completed treatment during a phase 2 research study. As I read this veteran's account,

I was struck by how grateful he was for the experience, which he credited with saving his life. He further described how he had struggled with survivor's guilt following return from the battlefield, after losing buddies who did not come home. Poignantly, he noted how he was, again, experiencing guilt, now because his fellow veterans were still suffering and unable to access this life-saving therapy. At that moment, I resolved to follow the data in support of this much needed therapeutic advance.

Approval for MDMA-assisted therapy will go down in history as a pivotal milestone, providing hope for many who are suffering from the ravages of PTSD. Alleviating human suffering is a moral responsibility. As the national suicide epidemic reminds us, time is not our friend. In closing, I am honored to submit this testimony in strongest support for the approval of MDMA-assisted therapy for treating PTSD at a time when our nation desperately needs it. Thank you for your consideration.

DR. NARENDRAN: Thank you.

Speaker number 26, please introduce yourself. You have three minutes.

MS. GROSH: Hello. My name is Sarah Grosh. I am a proxy reading a statement for Meaghan Buisson.

"My name is Meaghan Buisson. I'm a phase 2 clinical trial participant directly recruited into this study by Lykos. I was so scared of being touched, I initially turned them down. They called me again a year later. Desperate for help, I agreed. I moved to provinces [indiscernible] for the trial. The trial sponsor failed to obtain full informed consent. The day before my first session, they found an omission to my screening, which should have excluded me. Instead, Lykos broke its exclusionary criteria and kept me in the study.

"Regarding the assaults I suffered in the clinical trial, I will not be going into detail. There is a video clip widely available online. The fact that it and my name are public is extremely difficult. It should never have been necessary.

In September of 2021, I submitted a statement to the FDA as part of a formal complaint. In it, I made the FDA aware of abusive practices normalized by the clinical framework, and these practices included being blindfolded, gagged, pinned, cuddled, and caressed. All things I specifically indicated I did not consent to prior to MDMA dosing. Video evidence confirms physical and sexual assaults within those active sessions.

"I became suicidal during the trial, leading to a near missed attempt. Lykos was informed and chose not to document it. Undoubtedly, it was an adverse event and they hid it. The clinical trial shattered me. Overwhelmingly vulnerable, I was trafficked by my therapist whilst still in the clinical trial. The first physician to treat my wounds after I escaped said I was, quote, 'drugged, raped, blamed, and held as a sex slave,' end quote. Members of Lykos' leadership team, and principal investigator, and several phase 3 therapists witnessed my abuses firsthand. No one did a thing.

"Lykos still maintains that, quote,

'monitoring of study records throughout the course of the trial and afterwards did not indicate signs of ethical violation,' end quote. This is false. Even after my assaults, Lykos insists on employing unlicensed, unregulated individuals. This raises serious questions about ethics, patient safety, and informed consent. Vulnerable patients have no recourse when harms occur.

"What I experienced wasn't just too bad therapists; it was a predictable outcome of preventable harms and failures of Lykos. It is gutting to know that individuals in phase 3 have suffered similar harms, even after I alerted the FDA in 2021. I now struggle with new PTSD symptoms alongside my original ones. I suffer from crippling anxiety and a pervasive distrust of healthcare providers. These harms are magnified by Lykos' relentless efforts to skirt their responsibility by pushing a false narrative of misogynistic rape myths. This is disgusting and institutionalized abuse.

"The sponsor lied to the committee about

adverse events and safety monitoring. Trial videos must be independently reviewed. I urge the FDA to seriously consider its responsibility for patient safety and reconsider the veracity of Lykos' claims. Thank you."

DR. NARENDRAN: Thank you.

Speaker number 27, please state your name for the record. You have three minutes.

MR. CHESNEY: Hello. My name is Scott Chesney. I'm 54 years old and live in New Jersey. I was diagnosed with PTSD just one year ago. Thirty-seven and a half years after I awakened to paralysis, the result of a rare congenital arterial venous malformation, an AVM that erupted when I was just 15 years of age, there was no accident, no injury, and no physical trauma. After over a month stay in two different hospitals, exploratory surgery, and then 6 weeks in rehabilitation, I was contacted by my doctor, who finally shared with me the diagnosis and told me that I would never walk again.

Considering that my life was all about

movement and being a three-sport athlete, looking inevitably at an athletic scholarship in college shortly down the road, one would think becoming paralyzed would have devastated me; not me, physically. I just did whatever it took to get back into life by means of a wheelchair, hoping that I was just sick and regain movement in a few months.

Those constant thoughts of movement returning in a few months became a year, the year became a few years, and the few years have become close to four decades. While waiting, a wheelchair each morning next to my bed reminds me of paralysis. The hidden losses from my condition remind me throughout the day just how much has been stripped from my life. The loss of sexual function, bladder function, and bowel function are the hidden parts of a mobility disability, but are the more grueling reminders of living with a spinal cord injury.

Well, I've led an extraordinary life over the last 37 and a half years, getting married,

having two children, traveling to 43 countries, and so much more, deep-rooted sadness, depression, anger, and even rage within me finally rose to the surface. I can no longer suppress what that 15 year old had lost and what I have been missing for nearly four decades.

I can't help to wonder what this potential treatment you are reviewing today would have done for that 15 year old, and what it can do for this 15 year old now. As you consider your decision today, I'm hopeful that you will remember my story and the millions of veterans and non-veterans who also have compelling stories and are seeking a better treatment for their PTSD and could benefit greatly from this treatment. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 28, please introduce yourself. You have three minutes.

MS. PEARSE: Good afternoon. My name is Cristina Pearse. I was a participant in the phase 3 MAPP2 trial. I have no financial interest in this trial. MDMA-assisted therapy saved my

life. It is with gratitude that I share my story as it applies to so many others.

I was five when first sexually assaulted by a family friend. My childhood yields an ACE score of 9. As a young adult, I knew nothing of PTSD. I noticed symptoms once problematic. Over the next 40 years, I was diagnosed with depression, anxiety, and bipolar disorder. Doctors prescribed many, many medications, and I felt like a lab rat. Side effects were tough to navigate. One antidepressant energized me to attempt suicide.

After that, I was nervous about taking any drugs. I managed my disease with disciplined exercise and diet. I had some successes in life but suffered from failed marriages. I felt numb, I trusted no one, and I self-medicated with alcohol. I increasingly felt suicidal. Finally, when I was 45, I was diagnosed with PTSD, yet doctors offered me the same meds. I kept searching for new treatments and found this trial.

Within the very first hour of the MDMA session, I felt an intense sense of repair, a

spontaneous rewiring of my mind to body. The effects were immediate. The emotional flooding vanished. What used to feel like a tsunami of overwhelming panic was now merely a puddle at my feet; a changed perspective is everything.

If MDMA is a reset button, my skilled therapists were right there to ground my experience. Our therapeutic alliance fully unlocked this window of opportunity to process my traumas. It was hard work, but the results were life-changing. None of my previous therapies came close to unraveling all of my trauma.

The best aspect of this medicine is that I no longer need it. My MDMA training wheels are off and I remain resilient after those three sessions. I no longer need any medication, and especially not alcohol. PTSD is no longer my life sentence. Now, I'm in grad school studying clinical mental health counseling. I also founded Protea Foundation, a public charity supporting women's trauma recovery, because every 68 seconds, an American is sexually assaulted; every 9 minutes, that victim is a child;

and 91 percent of victims are female. Mine was never reported. Many victims never connect the dots to PTSD.

Each day we postpone this therapy, I ask at what cost? How many more people need to die before we approve an effective therapy? As you weigh the risks, please keep in mind the death rate for this understated population for perspective. This therapy can save many lives. I lost most of my life to this disease, I am grateful to reclaim it now, but I wish this was an approved medication decades ago. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 29, please state your name for the record. You have three minutes.

MR. POLIVY: Good afternoon. My name is Ari Polivy. I did not receive any compensation for being a clinical trial participant or for testifying here today. Thank you for your time. I'm 34 years old. I live in Hopkinton, Massachusetts. I'm a proud husband, celebrating 10 years of marriage this year, and I'm a father of

two little boys, 6 and 7 years old.

After growing up in the suburbs of Boston, I embarked on a journey in the Marine Corps as an officer and a KC-130J pilot in San Diego, California. That's the big cargo airplane that you see in my background. In 2017, after returning home from deployment to the Middle East, I began experiencing physical pain throughout my body when exposed to heat stimulus. It felt like fire ants biting my skin. It was unbearable. By 2018, I had tried many medications and therapies without any relief or hope of healing. I was subsequently medically retired from the Marine Corps, and my family and I moved back to Boston.

From 2017 to 2020, I attempted and failed many different modalities and therapies for both the physical and mental pain I was dealing with, paying out of pocket for many of them. My symptoms included anxiety; depression; suicidal ideations; insomnia; physical pain; and mood instability, making me want to isolate and be away from everybody.

By late 2020, I quit my job and told my wife and family that I needed help finding a way to heal. I had previously heard of psychedelic-assisted therapy from a fellow veteran but feared the safety and efficacy of going outside of the country to receive it. With what I felt was nothing left to try, I applied to the MDMA-assisted therapy phase 3 clinical trial in Boston. I started the initial screening, and then I had to wait 12 months because of the COVID pandemic.

In 2021, I mustered up the last bit of energy and effort I had to get to each trial appointment, uncertain if I'd make it to the next. The treatment provided a lot of what I thought was healing. I left the trial thinking I was healed and ready to enjoy the last rest of my life. I couldn't have been more wrong. Within 4 to 6 months of the trial ending, I found myself in a deeper, darker hole than I was in prior to the study. I learned later that I had received placebo and not MDMA. I was totally fooled. I had no idea.

It wasn't until I went through the crossover study and received MDMA that I finally have been able to heal and remain in a healed state beyond just a few months. I was able to experience the profound effects of intensive therapy only; however, the short-term impact of therapy-only speaks volumes to the necessity and need for MDMA to be a part of this process for long-term success.

MDMA is a critical component to bringing an end to the veteran suicide epidemic. I am often asked by fellow veterans on where to get help. As you're considering your decision today, I would ask you to remember my story and sacrifice, not only during my time in the Marine Corps, but also as a dedicated participant in the MDMA study. The veteran community who gives so much to this country deserves access to more options for care when dealing with these wounds that have such limited and ineffective treatments currently. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 30, please state your name for the record. You have three minutes.

MR. BLAKE: My name is Ron Blake. I'm not representing any organizations. PTSD is like having broken ribs; nobody can see it, but it hurts every time I breathe. I was diagnosed with PTSD following a trauma. Three men entered my downtown Phoenix loft while I was asleep one night. I was held down, beaten, and raped.

I represent myself daily as a tenacious survivor, but I've also been speaking out as an advocate for others on my ongoing nine-year, cross-country journey to recover from PTSD and to reach a symbolic goal involving a late-night comedy show. I gave a TEDx talk about how an unexpected moment of laughter from this comedy show stopped me from dying by suicide at 10:44 pm on November 2, 2015, sending me out on this now 79,000-mile adventure to learn how to process the trauma and to overcome PTSD.

Along the way, I've met 33,116 individuals, one by one, who have opened up to me about how they've been impacted by PTSD. They shared their powerful stories in 94 languages with 32 Sharpie

marker colors, on 506 giant foam boards. It is a massive collective story of struggles; isolation; heartbreak; loneliness; tragedy; and nightmares, but it's a lot more than that. It's an incredible collective story of moxie, optimism, and triumph.

I've received medical services for surgery and extensive physical therapy since this trauma. A violent crime victim compensation program assisted me with funding to restore some financial stability after I sustained $110,000 in trauma losses, but it's the PTSD part of my overall recovery that's been the most challenging for me.

A team of mental healthcare counselors and psychiatrists have worked with me over the years. I have had successes; however, the recovery continues to be a work in progress. I had a suicide attempt back on May 30th of 2015. Many of the people I've met on my travels from Newark, New Jersey to Yorba Linda, California opened up to me open about their own suicide attempts. Scores of these other folks shared stories of those we lost to suicide.

PTSD is formidable, but I am formidable, too, because I have a loving army of 33,116 individuals who've got my back, and I've got their backs as well. We are people from all walks of life. We are more than PTSD. All of these individuals hold out hope for the same thing I do, for additional treatments and viable options like the treatment you are reviewing today to help us move beyond the debilitating, injurious impacts of PTSD. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 31, please state your name for the record. You have three minutes.

MS. CASSELL: Hello. Members of the panel, I'm Katherine Cassell, Assistant Director of Veterans Health Policy for the Veterans of Foreign Wars of the United States. I nor my organization have conflicts of interest. On behalf of the 1.5 million members of the VFW and its auxiliary, we are honored to have been asked to be a witness for this hearing regarding MDMA when used in conjunction with psychotherapy to treat veterans

with PTSD.

For the first time in more than 50 years, the Department of Veterans Affairs is spending research on such compounds. Due to Lykos Therapeutics' study, there have been clinically significant results that will help our nation's veterans. It has been more than 25 years since any substantial treatments have been approved in the realms of treating mental health, which guides other medical fields that are driven by innovation and technological advancements.

VFW has participated in the PTSD working groups that have monitored the research conducted by Lykos and the change it has made in the lives of veterans. I mention this because it is a remarkable example of cooperation, collaboration, and teamwork. Lykos did its part by listening and acting to correct critical issues previously seen in MDMA treatments that impacted the safety of patients and ethical requirements of care teams. Additionally, they wanted to include veteran service organizations in the collaboration to

ensure the specific needs of veterans were being understood and met.

The VFW will continue to highlight the need for Lykos and others such as the VA to share data for their research, and maintain transparency to ensure the health and safety of patients. This should include a thorough explanation to the patient, along with a trusted family member or friend, of what the therapy entails, to include written consent prior to beginning any treatment, and additional consent during treatment to maintain the highest level of ethics.

PTSD and other mental health conditions can impact decision-making ability. By having a person that the patient trusts and has a daily impact on their well-being, this could help support positive change. A recommendation from this study is having a two-person support team, with a licensed therapist and a support person with good character and experience. Utilizing video methods can be intrusive and counter-indicated for people in need of PTSD care, as it is like surveillance.

VFW agrees with these suggestions, as it will protect both the medical treatment staff and the patient alike. This trusted health team approach is not an arduous task, as it is already used in the medical field, especially when looking at gynecological healthcare and other medical treatments.

In closing, the VFW does support MDMA psychotherapy and its approval, which will allow the extension of VA research on psychedelics to address veteran mental health. The men and women of the VFW have been impacted by PTSD, and we are encouraged by the results that we have seen in our members and veteran counterparts that have experienced this treatment. This concludes our statement. Thank you for your time.

DR. NARENDRAN: Thank you.

Speaker number 32, please introduce yourself. You have three minutes.

MS. TIPTON: Hi. My name is Lori Tipton, and I'm so grateful to be with you-all today. I have no financial conflicts of interest. I'm in

New Orleans, Louisiana, where in 2018, I participated in an FDA trial using MDMA along with psychotherapy for the treatment of PTSD. I was accepted into this trial after enduring PTSD for over a decade, stemming from a series of traumatic events. These included the loss of my brother to an overdose in 1999; my mother taking her own life and murdering two women in 2005, an experience that led me to discover their bodies; and aftermath of Hurricane Katrina's devastation just a month after.

After these events and before MDMA treatment, my life was filled with anxiety and hypervigilance. I was constantly afraid. I had mood swings; panic attacks; insomnia; intrusive thoughts; and suicidal ideations. I also lacked the ability to be present and to feel true joy. I felt less like the person I had been and more like a manifestation of the diagnosis. Recognizing my privilege, I was fortunate to have tried many things over the years. I had seen psychiatrists, psychologists, social workers, and therapists. I'd been prescribed antidepressants and anti-anxiety

medications. While these modalities did at times offer some relief of specific symptoms, nothing lasted or addressed my poor traumas.

I was very fortunate to be accepted into the Lykos trial after reading about it on social media and applying. Entering the trial, I harbored a healthy dose of skepticism, having tried numerous treatments in the past without success. What intrigued me about this trial was the potential of MDMA combined with a psychotherapy approach, which offered a fresh perspective beyond the constraints of traditional therapy.

Given the challenges posed by my PTSD, creating a sense of safety and openness to address and process my past traumas had been immensely difficult; however, MDMA became a catalyst, opening a pathway for me to explore a new outlook. Through this experience, I discovered the power of forgiveness, love, and self-appreciation, transforming not just my relationship with others, but also with myself.

While I wouldn't claim that MDMA-assisted

therapy completely eradicated my PTSD, upon completing the trial in 2018, I no longer met the diagnostic criteria, and that remains true today. I no longer endure the symptoms that tormented me for years, experiencing a newfound ease and laughter, and a profound sense of lightness, calmness, and reduced agitation. This transformation has made me a more effective partner, parent, and friend. What's most significant to me is the presence it has granted me, enhancing my enjoyment of motherhood. I am deeply thankful to MDMA-assisted therapy for reshaping and enriching my bond with my child.

While I acknowledge that MDMA therapy may not be effective for everyone, I strongly advocate for equal access to treatment for all individuals. I implore the panelists to consider the profound transformation MDMA therapy has brought to my life and to others as they weigh decisions that will carry far-reaching consequences. Thank you so much for your time.

DR. NARENDRAN: Thank you.

Speaker number 33, you have three minutes. Please introduce yourself.

MS. PLOTNICK: Thank you. Good afternoon. My name is Debbie Plotnick. I am Executive Vice President of State and Federal Advocacy at Mental Health America. Thank you for allowing Mental Health America the time today to speak to this important issue.

Mental Health America, or MHA as we're known, was founded in 1909. We're the nation's leading national non-profit dedicated to the promotion of mental health, mental well-being, and illness prevention. Our work is informed, designed, and led by the lived experience of people who are affected. Our national offices are in Alexandria, Virginia. We have 143 affiliates across the nation, many of whom provide direct care across the lifespan.

Approximately 12 million American adults are diagnosed with PTSD every given year. We know that the data gives us some glimpse into how many adults are formally diagnosed. The numbers fail to paint

a complete picture of the people who are affected by PTSD and trauma writ large, including those who do not seek out a formal diagnosis. Part of that is stigma and also because of barriers and lack of access to care.

Over the years, we at MHA and through our affiliates have listened to powerful stories like the ones you've heard today by people who are carrying the burden of PTSD. We've heard how it prevents people from thriving. They cannot be the parent, the sibling, the spouse, the artist, the student, the friend that they wish they could be. While currently available treatments do work for some people, it's actually few, and it's only some of the time. There's low efficacy and a lot of iatrogenic effects, and people feel, as you've heard from some of the people today, that they're failures instead of having been failed by the treatments that are currently available. They feel they might never get better.

We know that many individuals with PTSD are actively looking for treatments that will

positively touch their PTSD, and I say that as their PTSD because we know that the etiologies that cause their PTSD and the traumatic experiences are as varied as the people themselves. It is not just veterans; we've heard from many, many different people in many situations.

This is really evident in the data that we at MHA see in our very widely respected mental health reports, which come from our screening site, and it's recognized and cited in government studies and across the nation. We've offered free anonymous clinically validated mental health assessments to the general public since 2014. We've captured over 25 million screens for conditions like depression, anxiety and, of course, PTSD.

MHA's PTSD data offers an especially compelling rationale for incorporating patient insight and the burden of illness into treatment options and outcomes. Our screeners report many different types of trauma. We've heard about some of them today, and we know that the people are very

diverse.

DR. NARENDRAN: Thank you. Sorry. We're going to have to wrap this up. Thank you

MS. PLOTNICK: Okay.

There remains so much unmet need. That's why it is so important to consider and to approve novel treatments like MDMA therapy. We really appreciate the opportunity to talk about this, and we welcome more research and FDA expansion of options to people who are currently in great need, in dire need. Thank you.

DR. NARENDRAN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

We will take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topics during the break. We will resume at 3:57 pm.

(Whereupon, at 3:48 p.m., a recess was taken, and meeting resumed at 3:57 p.m.)

DR. NARENDRAN: Welcome back. We're just

going to give the sponsor two minutes to answer a couple of the committee's questions so they could respond to it.

DR. YAZAR-KLOSINSKI: Thank you for recognizing us. Dr. Lilienstein will address one of the questions.

DR. LILIENSTEIN: Dr. Lilienstein, Lykos Therapeutics. There have been a lot of conversations amongst the panel today and discussion around this treatment modality and the therapy component of it. I wanted to recognize that this is a complicated application. It's a drug plus therapy, and the drug is in FDA's purview, but the therapy, that's a new component, something new that we're considering; how do we combine these two and move these two forward in a responsible way? In many ways, we're creating a new field of medicine as this moves forward, and we don't take that lightly, so a really significant responsibility, the drug and the therapy.

I was the medical monitor on both of the two phase 3 clinical trials, so I personally also take

this very, very seriously. We take all concerns around harms and clinical trial conduct and research conduct very seriously as well. But amidst the complication of all of this, there are patients, and patients deserve us to work hard to figure out how to move something complicated forward, and only in the context of a regulated product is there really the chance to move forward and move the system forward. Thank you for your discussion today and for your time.

Questions to the Committee and Discussion

DR. NARENDRAN: Thank you. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while the meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning the

wording of the question. We will proceed with our first question, which is a discussion question.

Question number 1, discuss the evidence of effectiveness for midomafetamine for the following treatment of posttraumatic stress disorder. Consider the following: the potential impact of functional unblinding on interpretability of efficacy results; the durability of effect; the role of psychological intervention in the treatment paradigm.

Are there any questions about the question?

Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA. For the agency, we see discuss the evidence of the effectiveness of midomafetamine, so do you mean the drug plus the proposed psychotherapy and not just the drug alone?

DR. FARCHIONE: This is Tiffany Farchione. I think it's fair to comment on either.

DR. NARENDRAN: Any other questions about the question?

(No response.)

DR. NARENDRAN: Okay. Does anybody want to go first?

Dr. Dunn? Thank you.

DR. DUNN: Walter Dunn, UCLA, VA. Regarding the first question about the potential impact of functional unblinding, as was mentioned previously, this is a known issue with medications such as MDMA and other classical psychedelics. I think it does degrade my confidence in the efficacy results a bit, even perhaps some of the safety issues. The main concern for me is the functional unblinding, with the expectational bias, with potential misconduct. I think if you line up all those three things together, that is the major issue for me. So regarding misconduct, it sounds like the agency is investigating that, so I trust that they'll do a thorough job on it.

Unfortunately, for the expectation bias, we don't have any data on that. As my colleague, Fiedorowicz, alluded to earlier when he asked about that, this was not data that was obtained during the trial, so we don't know the expectation bias of

the subjects, of the therapists, or even actually the independent raters. So perhaps this is something that, for future psychedelic trials, maybe the agency wants to consider, as I think that would play a role, especially in its interaction with the functional unblinding aspect of it and interpreting the efficacy results. That's my comment on that.

In terms of the durability of effect, the two main issues pose a potential threat to the MPLONG data in my mind; number one, again, the misconduct, again, patients being discouraged from participating in that study. Then also, as I mentioned previously, the shift parameter analysis I think should include any type of treatments that would address any potentially worsening symptoms. It sounds like this analysis was only done with psychedelic compounds, DMT, MDMA, and ketamine, but I think the psychotherapy, the SSRIs, are fair game as far as taking those into consideration because I think if you don't, it, again, artificially inflates the durability of the MDMA treatment.

Then as far as the role for the psychological intervention, I mean, that is I think one of the key issues today. Obviously, we don't have a 2-by-2 factorial design, which would make the question easier to answer. And again, this is not something under the purview of the FDA. And even beyond that, as we've heard from the public commentary portion, there's some serious questions about the sponsor being able to educate and deliver the psychological intervention in a responsible way.

Now, not to say that everybody from Lykos or everybody involved in the trials engaged in misconduct. I know for sure that most of those folks only had the best intentions of the subjects at heart but, unfortunately, there potentially has been some misconduct that's occurred, potentially a few individuals that really have polluted or corrupted our ability to really interpret the data. So those are my comments on the three discussion issues. Thank you.

DR. NARENDRAN: Next, Dr. Holtzheimer, who's

virtual.

DR. HOLTZHEIMER: Thank you. Again, Paul Holtzheimer from the National Center for PTSD. I echo a lot of Dr. Dunn's comments, and I share concerns about the conduct of the study, but I'm going to limit my comments now to the data presented to us.

The functional blinding clearly occurred. That leads to the strong reality that expectation bias played a part in the outcomes of the study, and again, stating the obvious, but expectation bias can work in two ways. It can exaggerate the effect of the active treatment. It can also blunt the effect of the placebo treatment.

The change that I'm speaking, especially to MAPP2, the difference between the active and the placebo group is statistically significant by their analyses, but relatively small enough that I think the role of expectation bias cannot at all be discounted as potentially accounting for a lot of that difference. So I'm unconvinced by the acute efficacy of the treatment as demonstrated by these

data.

I'm also not convinced by the durability data, again, because of the use of other treatments by a substantial portion of the follow-up group, and then I think the psychological intervention is still, for me, a bit of a black box. It's not clear exactly what was done in each session. I believe the sponsor, they assessed this in the trials; however, what's described as, really, a relatively vague, ill-defined treatment, psychosocial intervention, I think it would be hard to standardize across arms. And I'm not convinced that it was equal across arms, which could further contribute to differences and outcomes between the groups. Thank you.

DR. NARENDRAN: Thank you.

Dr. Barone, you're virtual.

DR. BARONE: Hi. Melissa Barone, VA Maryland Health Care System. I echo a lot of the concerns that have been discussed already, and I won't belabor them. I think there are a number of things that make me question how robust the results

are. I think they're really promising, and it sounds like MDMA and this treatment have really impacted a number of people in positive ways, but it seems like there are so many problems with the data. Each one alone might be ok, but when you pile them up on top of each other, when you've got unblinding and there are tons of compounds, and the durability data, there's not enough data on diverse populations or people with severe PTSD. So I think there are a lot of questions, still, that I would have about how effective the treatment is and how durable it is.

As far as the psychotherapy intervention goes, the way that it is presented in the application makes it impossible to disentangle the two. MDMA is not administered without the psychotherapy, and the psychotherapy is really vague. It is not well determined. It seems like it was not standardized, and that makes it really hard to determine how effective it is, how safe it is for patients in a really vulnerable state when they're under the influence of MDMA.

The other thing I think about is that we already have evidence-based treatments for PTSD, and yes, they do have dropout rates. But they do have really strong outcomes, and those treatments usually take around 12 hours of therapy. They're covered by insurance, so lots of people have access to them, and they do have strong outcomes. So when you think about that compared to a treatment that's got 42 hours of treatment, how do you even compare them? What is the burden on access? What is the burden on providers to be providing that treatment when we already have treatments that are really effective? Thank you.

DR. NARENDRAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Hi. I'm going to try and go through these bit by bit. I would say, based on the data, I'm somewhat convinced of MDMA's effectiveness. I think this is a promising pathway. I think most of us probably think that, and I'm really pleased for those that it has helped. That said, in terms of this study and this trial, I'm concerned about the unblinding of

therapists and how that impacted what they were doing in a session.

I'm really concerned with this lack of real inclusion of BIPOC participants. Like I mentioned earlier, there's information that says that, yes, it seems to at least help people more if they're white, and some of these effects seem to disappear if they're not; and the fact that this study has so many white participants I think is problematic because I don't want something to roll out that only helps this one group.

I have real concerns with the validity of the data and the allegations of misconduct, especially as a patient representative. I want everyone who has had success with MDMA to know that I have heard you, but also, I can't in good conscience support something where these many harms are being reported and just say, "Oh, someone somewhere is investigating it, and I'm sure it will be taken care of." I think patterns of institutional violence that we've seen, things that don't get addressed, we learn this over and over

and over, and it doesn't often change, so I think it's important that that has to be called out.

Then also, I struggle with the fact that 40 percent of the people that were in the MDMA-assisted therapy arm were previous users. To me, that really stacks the deck towards improving efficacy because we can assume if you had a terrible experience, or it didn't do anything worthwhile for you, are you going to go through the effort of being in a clinical trial? And it also stacks the deck for seeing less adverse events, so that I find problematic as well. So that's some of the thoughts that are rambling around in my head at the moment.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Thank you. Jess Fiedorowicz, University of Ottawa. The treatment effects observed in the study were large, and it was encouraging to hear the stories of those who reported improved outcomes, and great to hear that. Ordinarily, these effect sizes would reassure me

about bias, but the level of interest, even people referring to this as a movement, the large number of people with prior treatment presumed very high expectancy of benefit that wasn't measured and allegiance of those I think is unlike most things that we see, and I think that warrants some consideration.

We see several pearls of evidence for that. The high frequency of MDMA use compared to the background use in the general population is extremely high, a very low dropout rate in spite of a very involved treatment that required fasting, prolonged in multiple sessions, that's not the sort of dropout we would typically see, and that would suggest a very high level of interest, engagement, and allegiance.

Then there's a potential, we talked about, for therapist unblinding and how that benefits the treatment itself that's being provided in these very long sessions, so I think it's certainly possible that that bias could be large enough to explain that difference, or at least certainly

beyond the threshold by which we might think it's clinically significant.

We had some questions for the agency this morning that apparently did not come back, including questions about recruiting, sex, or other differences on risk that we didn't hear back from. That would also be important to inform the decision. The allegations of misconduct were quite concerning for me, all of them, including those related to data validity, and we'll defer to the investigation for that. I don't think it warrants more discussion. Thanks.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Kim Witczak, consumer rep. For starters, I am pleased to see at least this treatment being something that we're looking at and hearing from some of the members of the public that had positive -- but at the same time, with that being said, I have to say I'm pretty concerned with the misconduct, the allegations, because usually that happens after something's on the market and it

happens in lawsuits, and we have the advantage of now being able to go in and further investigate. So I would really like to hear more about that because I'm afraid that could impact the ability to eventually use this substance for other -- we heard with the the VA groups that want to see it out there. So that is one thing I think we need to look at.

The unblinding, the functional unblinding as we look at these treatments, I think we do further investigations, whether it's this one or something else, because you said to address -- I would say that we have to figure out -- I know you guys recommended something, and they came back and said they didn't want to do it. So I feel like we -- otherwise, we're going to continually be in this situation.

Then, we are in this new environment. There's a movement, there's a lot of hype, so you're going to automatically have more -- it's going to attract more of those people that want to be a part of this. So I think that is something

that we have to take in consideration. Then I have to say the whole therapy as part of approving this medication, without knowing and seeing it -- even do an independent review of some of these videos. I do think that's an interesting suggestion, is have you looked at those? Do you know what they are? And if it's not you, if it's an independent -- because the therapy -- and we didn't have the comparative arms to look at either. So all of those impact and could affect the effectiveness that we see with these trials. Thank you.

DR. NARENDRAN: Next, Dr. Rebo.

DR. REBO: Thank you. Elizabeth Rebo from Kaiser Permanente. I echo and share the same concerns that everyone else has articulated, so I don't see a reason to rehash that again. I will say, with what Kim just said in regards to advice that was provided by the agency and not accepted, I was surprised to see that. I don't really understand why there wasn't a desire to capture some of the positive side effects, if you will, and

be able to have that, and look at it from an abuse potential. I was very happy to see that there are patients that have benefited from this, but I do have a lot of concerns with the integrity of the trial, as was presented.

One thing I did want to say just in regards to the psychological intervention and there being concerns with that being different patient to patient, I can understand those concerns, but at the same time I do think that you have to address the situation as it's occurring, and that's going to vary patient to patient. I don't think that type of standardization could even exist because you have to address the immediate concerns of what's happening at the moment, and there's no way to really standardize that. So I just wanted to call that out since that was articulated as a concern. Thank you.

DR. NARENDRAN: Dr. Hertig?

DR. HERTIG: John Hertig. One of the benefits of going in the latter part of this discussion is I get to echo the really brilliant

comments from my peers, and I do so, but I also want to make a couple fine points. One is, I do commend the agency, as well as the sponsor, for looking at these new novel therapies for real need, and I'm excited and hopeful by some of the efficacy results, as well as some of the stories that we heard from our friends and family.

That said, I liken this a little bit to we're building the airplane while we're flying it, and I'm ok with that when it comes to things like functional bias, particularly when we're looking at psychedelics. I can deal with that. But what I can't really deal with when we're building that airplane are the safety concerns, and we're going to talk a little bit more about safety concerns in a different discussion. But some of the safety issues, and gaps in data, and other issues related to safety are things I really can't necessarily look past, and I'll save my comments for that section of the discussion. Thank you.

DR. NARENDRAN: Dr. Canuso?

DR. CANUSO: Carla Canuso, industry rep, and

I share everyone else's sentiments, both the promise and the caveats of this treatment. But I do think that we should note, when we talk about effectiveness, we also have to consider generalizability, and it struck me that more patients in this program had prior exposure to MDMA than they had to standard SSRI treatment prior to entry into studies. So it does call into question how this drug will be effective in a more general clinical population, presumably those who have received standard treatment or have failed standard treatment.

DR. NARENDRAN: Dr. Iyengar?

DR. IYENGAR: Satish Iyengar from Pittsburgh. Ordinarily, when I see studies with both therapy and drug, a 2-by-2 design that is quite common, here, to me, it makes no sense because the therapy is so integral to the treatment. It's just only one column that's really needed.

The other point that I wanted to make, actually, it's a question. Dr. [indiscernible]

referred to this as going into new medicine, and you talked about building the airplane as you're flying it Because of the integralness of the therapy in the treatment, it seems to me there has to be some way to get that under the umbrella of the FDA. Is that just out of the question or can you make a special case out of this?

(Dr. Farchione gestures no.)

DR. IYENGAR: That's all.

DR. DUNN: Walter Dunn, UCLA. This is actually a question for my colleague, Dr. Barone. A lot of the discussions surround the efficacy of this treatment compared to our standard treatments, and one of the recurring topics is this idea of dropout. And certainly we know that in clinical practice of trauma-focused therapy, we have a high degree of dropout, but in the clinical trials, for things like PE and CPT, my understanding is that in the 12 or 15 sessions, that there actually was not that high of a rate of dropout.

So I'm wondering if we're comparing apples to oranges here when we keep citing that as a

reason that we need a new treatment because our current treatments have high dropout, but my understanding is that in those controlled trials of those psychotherapies, dropout was not a major signal.

DR. BARONE: Yes, that's a great question. The dropout for PE and CPT is definitely higher than MDMA. Their lack of dropout is remarkable. I've never seen anything close to it, which does make me question the selection bias and other, like expectancy bias, things that might have contributed to that. So there is a real need to really engage with patients, really explain the rationale, and help them understand why the treatment is going to be helpful so that you can keep them connected or keep them in the treatment and help them work through it. But the dropout is a little bit higher than MDMA.

Does that answer your question?

DR. DUNN: Yes. So in the clinical trials for PE and CPT, their dropout rates were still higher than what we see with MDMA.

DR. BARONE: Yes.

DR. DUNN: Okay, but probably not a [indiscernible] or possibility to expect that if this were deployed in a clinical context, that we would see higher dropout rates than we see in the clinical trials for this treatment.

DR. BARONE: Right. Like I said, the recruitment issues, and concerns, and questions really limit the generalizability of this data to what we would see in a clinic, so I'm not sure that we would see the dropout rates that Lykos is presenting in real-world clinics.

DR. DUNN: It makes sense.

And one additional comment about the psychological intervention, this was actually raised by Ms. Witczak a little bit earlier about the psychotherapy and if it was proprietary to Lykos. Unfortunately, I didn't get a chance to ask this, but my understanding is that even though the psychological intervention isn't a manual that's publicly available, taking a look at it myself, Lykos would be the one delivering this QHP

education, and they have control of the drug.

So I don't know what their plans are -- and again, this is probably a commercial question, not regulatory -- but if they're the the sole gatekeepers of this psychotherapy training, and only if you go through their training will they give you access to the drug, I could potentially see that as problematic.

I think when a single entity holds the keys and the power to everything, it can get distorted, you don't get different perspectives, and potentially, this is why some of the abuses or misconduct occurred because, again, this was in the hands of a few individuals. So again, I think this is out of regulatory purview, but trying to disentangle the question of Lykos versus the treatment.

Again, many of the critical comments from the public were not necessarily about the treatment itself, but more were aimed toward Lykos, and I think we shouldn't associate one in the same. And if we're able to disentangle the two, I think it

would provide you more assurance about this being rolled out in a safer manner.

DR. NARENDRAN: That's a little bit outside of this scope.

I just want to hear from Dr. Amirshahi.

DR. AMIRSHAHI: Thank you. Maryann Amirshahi, Georgetown. I have to disclaim that I am not a psychiatrist, and I struggled a bit with this question because this panel has been very unique to me. As a toxicologist, we usually do assessment of efficacy and safety. Perhaps you could provide some guidance to me and members of the panel that are less familiar with the psychiatry behind this.

I will say that I think that there is an efficacy signal, but I think that efficacy signal is denuded by a lot of these confounders that my brilliant predecessors have already discussed. But perhaps there's a way that we could better study because what I struggle with is the relative contribution of the psychotherapy.

For example, if you have an efficacious drug

but a very poor therapist, you may have a similar effect for somebody who responds poorly to the drug but has an outstanding therapist. So perhaps we need a larger sample size with more structure, not necessarily prohibitive therapy -- and once again, this is a little out of my lane -- to perhaps better quantify the relative contribution of the drug in a meaningful way. Thank you.

DR. NARENDRAN: Thank you. That was an excellent comment.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: One thing I did want to mention it would be -- and I am. I agree with being way out of my lane with this one, but I just kept thinking as I was going through this, what would MDMA -- looking at it with comparators of doing it with CBT, doing it with EMDR, doing it with some of the evidence-based things, and seeing are there differences, are there similarities. I feel like this is really narrow when therapy plays such an important role.

Then just a quick comment on functional

unblinding for participants, as someone who has PTSD, I think that there are impacts with that, but also there are a lot of pieces of PTSD that in a sense -- especially when you talk about the freeze response or the fight-or-flight response -- are much more, in some ways, stimulus response. So I think in that way, it would be hard, even with unblinding, to be, "Well, are you startling me less? Are you startling more? Well, do I jump every time my husband walks into the bathroom?" These are real effects that it has. "Am I checking the locks a bunch of times?"

So there are things with PTSD that I think are a little bit more ingrained in terms of how you manage life and work through life, that I'm comfortable with the functional unbinding in that regards for the participants, whereas not as comfortable with it for the therapists.

DR. NARENDRAN: Dr. Holtzheimer, virtual.

DR. HOLTZHEIMER: Thank you. Again, Dr. Paul Holtzheimer, National Center for PTSD. This is just echoing and expanding a little bit on

some prior comments related to the therapy. Typically, when I think about evaluating the data for an adjunctive or augmentation therapy, it's a medication or device, or something that's being added to a treatment that's already standard of care and already has been established in terms of its efficacy clinically; and just to make the obvious, obvious, I think the challenge here is that the psychotherapy itself in this case is not evidence-based yet, so it's not standard of care, we don't know how well it works on its own, and the idea of then augmenting it with another agent is hard to interpret.

Again, to ask the FDA to do that is not appropriate. Typically, FDA would be doing this with something that's, again, standard of care, and then looking at an adjunct. This is not standard of care, and I think that's a major downside of the application overall, is that the therapy itself is still, I would consider, experimental.

DR. NARENDRAN: The agency, go ahead.

DR. FARCHIONE: We just want to follow up on

a previous issue, if we can pass it over to Dr. Stein.

DR. STEIN: Sure. I just wanted to get back to the point that Dr. Dunn raised. The intent of this, if this is approved, the labeling would not specify the specific type. It would describe at a high level the type of therapy that was provided, psychotherapy that was provided; it wouldn't specify or require that prior therapy. And likewise, the REMS, I think you've heard the elements of the REMS which would require certified healthcare sites, ability to monitor, licensed therapists, the elements that you heard. It wouldn't specify a particular approval of a type of therapy that the therapist was licensed to deliver.

So if you're asking would the labeling or the REMS in some way restrict a particular therapy, as I said, neither the labeling nor would I think the REMS would specify to that detail.

DR. NARENDRAN: Thank you.

In terms of my comments, I do have to say, one of the things that I kept thinking is how many

drugs have been approved if we had this level of functional unblinding on the interpretability of the efficacy results. I mean, they could have probably had tons of psychiatric drugs that are approved, this level of expectation bias, because 40 percent of them already know they probably had a good experience and they enrolled selectively; and then they come in and they believe it's going to work. Many of you have echoed that.

So to me, I'm not convinced at all this drug is effective based on the data I saw. Unless you can somehow build in the model for expectation and selection bias is incorporated into it, I'm not convinced that this drug is effective in the short term. Durability of the effect, unless you've taken multiple data points -- PTSD is a disorder where symptoms can fluctuate quite a bit, we all know that, and I feel like there should have been more repeated assessments over time to really gauge where these people are heading.

I think there's also a sub-sampling of two different studies in two different timepoints

spread across. I'm not convinced about that at all. And the psychological intervention, I clearly echo my colleagues' comments that I didn't feel it was structured. It would have been nice to have some sort of CBT, or some pick one EMDR, and everybody got that, and a 2-by-2 design to really understand, and maybe that would have helped with some of this expectation bias and selection bias issues as well.

So going forward, for psychedelics to be approved, I think there has to be a more complex model and think outside the box of the regular double-blind, placebo-controlled trials because I don't think this is an adequately controlled trial, by any means, to approve. That's my personal thoughts.

I'll summarize what I heard from the panel.

Are there any other comments anybody wants to add to?

(No response.)

DR. NARENDRAN: Okay.

In terms of summary, I heard people did feel

there was functional unblinding, and expectation bias played a role. People felt the misconduct also added to that and diminishes the efficacy results. I also heard that some people felt there is definitely an efficacy signal, and some people felt, at least for some participants, it seems to have helped, and that did come across in the data. I also heard that a larger sample size would have been better to really understand some of these issues. I heard also that the expectation bias and functional unblinding in itself could account for what was seen in the clinical trial in the short term, from other people as well.

With respect to the expectation bias and selection bias, people raised concerns that 40 percent of the users were MDMA users, there was such a low dropout rate, and they were probably selected to do better on MDMA. I also heard that maybe the unblinding of the subject is less important, but the unblinding of the therapist during the course of the sessions could have played a bigger role on the final efficacy measure that

came through.

In terms of durability, I felt there is universally more skepticism on the durability. People felt participants were discouraged from enrolling into it. Perhaps the shift parameter should include other variables like psychotherapy, SSRIs, and psychostimulant drugs, and I heard many people say that they were not convinced about the durability, and I also heard that there were too many compounds involved to really tease that small data set apart.

In terms of the psychological intervention, people felt it should have been structured. It should have been a 2-by-2 factor design to understand it better. Again, I heard concerns about the therapist blinding, and probably some power of suggestibility towards the rating scale dates could have influenced the results.

Is there anything else anybody wants to add to the summary, panel members?

(No response.)

DR. NARENDRAN: No? Okay. If not, we can

move to the next question.

Jess, go ahead.

DR. FIEDOROWICZ: Yes. I'll just quickly add, I tend to be a strong proponent of 2-by-2 factorial studies, in general, but I'm kind of with Satish on this comment here given the theoretical underpinnings of this, although there may be other ways to try to address or tease things out.

DR. NARENDRAN: Usually, we don't allow the sponsor to talk during this time, but we'll just give you a quick second to rebut.

DR. YAZAR-KLOSINSKI: Thank you. I did want to clarify my earlier comment that the medication sessions were standardized based on adherence criteria. These criteria were rated by independent observer clinicians. The agency's points about the variability primarily applies to the integrative psychotherapy sessions that do not include drug, so I believe that might help with understanding some of the difference in interpretation.

DR. NARENDRAN: Thank you.

We'll move to question number 2. Question

number 2, discuss whether the available data are adequate to characterize the safety of midomafetamine for treatment of PTSD. Consider the limited data collected on events deemed positive, favorable, or neutral that would inform abuse potential for this program, and the lack of data for some of the clinical laboratory tests. Comment on whether you have concerns about other safety issues and what additional data would be useful to characterize the safety of midomafetamine.

Any questions about the question?

(No response.)

DR. NARENDRAN: No questions about the question?

(No response.)

DR. NARENDRAN: If there are no questions about the question, anybody to volunteer to go first?

Dr. Dunn, I'm glad I can count on you.

(Laughter.)

DR. DUNN: Walter Dunn, UCLA, VA. Regarding the first bullet point about the lack of data for

clinical laboratory tests, my concern would be, if this was rolled out clinically, you would have patients who would require, from a clinical standpoint, more than three sessions. Obviously, we know from the PE and then the CPT trials that these were 12 to 15 sessions, but in reality, patients need much longer treatment courses than that. So even though the early phase 2 trial suggested that, there was no additional benefit after three.

Again, it's from a limited sample and, again, a clinical reality that when you have multiple comorbidities, especially patients who would have been excluded from the initial phase 2 trials, you're going to have patients exposed to more than three medicine sessions. So again, I think that's something that probably the REMS would address in that this will be an ongoing real-world data type of situation where we can collect data on that. So I would highlight that to the agency as being something to keep a focus on.

Then, of course the second bullet point

about safety issues, again, boundary violations, ethical misconduct, really characterizing beyond the acute whether these things are going to occur, or if they're going to occur, I think the same issues apply to what's been raised about the clinical trials, where folks have been discouraged, or they may be reluctant to report these boundary violations because they may threaten the whole movement towards approving psychedelic-based studies.

So I don't know how we can get that type of information, but I would say that perhaps the agency works closely with the state medical boards to see what type of complaints are being made about therapists, potentially, crossing boundaries or being coercive. Again, this is really based on the effect of the drug. It's designed to make you closer to another human being and, unfortunately, that can be taken advantage of. Thank you.

DR. NARENDRAN: Dr. Holtzheimer?

DR. HOLTZHEIMER: Walter covered a lot of what I was going to say. Again, Paul Holtzheimer,

National Center for PTSD. I think there are some clearly missing safety data that would be necessary to ensure the long-term safety tolerability of this intervention. That said, given the results of the clinical trials, I'm pretty comfortable this could be done with postmarketing surveillance, and the REMS system I think looks adequate to capture a lot of that.

I'm most concerned about, as Walter mentioned -- Dr. Dunn mentioned -- the issues with patient boundary violations and all the rest, and this happened in a very highly controlled clinical trial; hopefully not much, but apparently reports are that it happened to some degree. I think there is concern, as this is rolled out to a larger population of clinicians, how that will be monitored and how that could be controlled. Again, it's not our job necessarily to do that; just I do have concerns about that. Thank you.

DR. NARENDRAN: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi, Georgetown. As a toxicologist, I feel a lot more

comfortable that this is in my wheelhouse. I do feel that there are significant holes in the data. In addition to what you mentioned, I'm thinking about laboratory parameters, particularly with long-term use as far as hepatotoxicity goes. In addition, we talked about hyponatremia and drug-drug interactions for common medications. The fact that there were inadequate QTc studies performed I think are also very important. Additionally, the fact that the agency had recommended specifically to look at abuse liability and potential, we didn't follow those long term I think is one of the most important points that we need to focus on.

Then secondarily, as far as another safety thing goes, with regard to how we are going to set up a safe environment for these patients, and particularly with structure, for example, a lot of asymptomatic hypertension does not need to be treated or evaluated in an emergency department, so we have to ensure that the patients that are getting these treatments have adequate clinical

judgment and oversight; somebody who may be less comfortable such as a therapist with asymptomatic elevated high blood pressure may send that person to an emergency department, which would be an unnecessary use of healthcare resources and can further undermine the therapy and the therapeutic relationship.

So I think all of these things really need to be explored to come up with a good safety plan, and I think because this is new, this is the first panel, from my understanding, that we're looking at psychedelics, a lot of what we may do may become precedent, and we have less of a reference for lessons learned from previous things. So I think we need to proceed cautiously. Thank you.

DR. NARENDRAN: Dr. Hertig?

DR. HERTIG: John Hertig, again echoing the comments from my colleagues here, and I do have the same concern around some of the gaps in the safety data. I do believe that phase 4 pharmacovigilance work can help us fill some of those gaps.

I am particularly concerned about the

limited data around positive or favorable response and that leading to abuse. Drug diversion is a major issue in a variety of different controlled substances. I think if and when this were to be approved, there would be a subset of the population that would want it regardless of clinical need, and the traction to have a form of this medicine that isn't on the street and not potentially laced with other drugs may lead this to be another diversion risk, and I don't think we've fully vetted out how to manage that or understand that, given the limited data that we've been provided. So for me, that's another public health or patient safety issue worth discussing. Thank you.

DR. NARENDRAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you.

Dr. Joniak-Grant. In terms of safety, again, 40 percent of previous users, I think that would make the safety profile look better than it is. We never did get the information from the sponsor on why some of the participants chose to discontinue or withdraw, so I'm still curious about that.

Again, the lack of diversity in the study population, because there could be certain groups that would be more prone to adverse events, may be at higher risk for cardiovascular events. And I am concerned with this cardiovascular safety with this increase in blood pressure and heart rate. With COVID, we've seen quite a rise in dysautonomia diagnosis and POTS, and I'm wondering how that would come into play with elevated blood pressure, and heart rate, and tachycardia, so I think that's something that needs to be looked at more.

When I was looking at some of the data on the treatment-emergent adverse events, there were reports of ones that hadn't resolved in 7 days -- paresthesia; tremor; myalgia; nausea; hypoesthesia; muscle tightness -- that was still going on 7 days after, just kind of left there on a table with no further information. Did they ever resolve? Have they resolved? How were they handled? What did that require of the participants? So I think more information about that is important.

Then with this lack of collecting the positive favorable feelings, I come at this from two angles. One, I wonder, given the treatment approach -- which, granted, I don't know a lot about with this therapy -- this idea that you're pushing through distress, and the distress is a good thing, were certain symptoms like distress not collected because they were seen as therapeutic? They were seen as a positive thing. They were seen as making positive steps. So I'd like to have an idea would there be some that laypeople would see as negative but the team decides, "Well, that's actually really positive," and how does that play out for collecting data.

Then on the other hand, for these positive and favorable feelings that we would see as euphoria, blissfulness, things like that, for me, I'm a little less concerned about abuse of the drug. It's infrequently noted as a drug of abuse. I think we want to be mindful of it, but I think that there's a lot of literature that makes me less nervous about this one. But these positive,

favorable feelings I think make the situation very rife for there to be abuse of a patient, particularly for clinicians that are looking for vulnerable patients and, unfortunately, they do exist.

So for me, that's the big piece of it, is being at risk in the interaction with the clinician and being at risk with the outside world if you're discharged too soon. There are really no details, as it was pointed out by FDA, when a session is over and when it's safe for a patient to go home. I think having objective criteria for what that looks like is really important.

I don't think I'm the only person who's come out of twilight, and it's the end of the day, and they're like, "Oh, sure, you can go home," and you can hardly walk sometimes, and you're wobbly, and they're like, "Well, let's get you in a wheelchair," or when they send you home from having your wisdom teeth done, and no memory of what happened or what you said.

So with something like this, I think we have

to really make it very clear what it means for someone to be ready to go home, especially in light of the fact that, in the study, a lot of them stayed overnight. So maybe it's not even necessarily about length of time, but is there something about sleeping that can reset it? I know a lot of patients that have migraines and say their migraine doesn't go away until they get some good sleep, even if it's only an hour or two; so understanding what that looks like for patient safety I think is important as well.

DR. NARENDRAN: Raj Narendran, and I'll add my comments. There's a lot of missing data. I don't know how you would characterize the risks. To me, the cardiovascular risk is still very high. It's just not well characterized; the hepatotoxicity lab values. I would also really want to see the EKGs at discharge because if you had done discharge EKGs, you would have had, left and right, all kinds of things. I just know this because I use amphetamine at high doses from my research subjects, and there are all kinds of EKG

abnormalities. So when you go into large-scale, uncontrolled populations with multiple comorbidities, you're going to have a ton of problems on your hand. I just don't think a REMS can adequately address some of this.

I'm also super concerned about the abuse liability. I think there will be left and right diversion. Illicit MDMA is going to soar because it's going to be all over the map, so I think you have to be really careful. I think we really need to characterize the abuse liability and the diversion risk. You also have to characterize the cardiovascular risk and the boundary violations, and things that can go down that are also concerns. It will be very problematic. That's personal, how I feel. The lack of data doesn't support the evidence that there won't be problems. There are a lot of holes in this data set, so I think I would want something really characterized before we go forward.

Anybody else have comments?

Ms. Witczak?

MS. WITCZAK: Kim Witczak, consumer rep. I would like to reiterate a lot of what has already been said, but I will say the suggestibility relational harms are really concerning to me, as well as the environment in which this is going to operate, because you've got to realize that clinical trials are usually the best of the best situation, and that is not what's happening in the real world.

I always go back to what's going to happen in the real world, just like all the stuff with Ozempic. We have Ozempic clinics, we've got health clinics; everybody's in the business now because of the commercialization. And I know that's out of your -- but I think we do need to be concerned about those things, especially when it goes into where everybody wants to take a piece of the action. So I think those are things that are concerning to me. Thank you.

DR. NARENDRAN: Yes. I would not be surprised if people go home and use cocaine, use alcohol with their partner, who's supposed to be

responsible. You're going to have left and right issues. That's my personal feeling on it. You can see it coming.

So let me try to summarize the committee's discussion. The concerns about boundary violations were raised, power, suggestibility, and relationship harm that could happen. Also, some people felt that it could be done safely in the short term as done in the clinical trial, although there was clear agreement that to do multiple sessions over long periods of time, the data is not there to probably support it. Many of the members echoed that in the short term, this could be done safely, although they wanted to see more data and how it would go with comorbid populations.

I heard concerns about the hyponatremia, lack of lab data, lack of QTc data, cardiac data, although many people thought that that could be addressed through the REMS and a REMS can support that. The abuse liability was felt to be inadequate. Concerns about diversion were raised, so that's something that would also have to be very

carefully looked into. But many folks, once again, thought the phase 4 data can address a lot of these issues.

Lack of diversity was raised. Perhaps some populations, diverse groups, could be more at risk for cardiovascular concerns was raised as well. There's also concern about a lot of the adverse events not being perhaps recorded correctly as a concern because it was thought to contribute to the therapeutic effect.

Is there anything else you guys want to add?

(No response.)

DR. NARENDRAN: If not, we can move to question number 3. Question 3, discuss the potential for patient impairment to occur with midomafetamine and the potential for serious harm that may result due to impairment.

Anybody want to go first?

(No response.)

DR. NARENDRAN: Go ahead, agency.

DR. BURACCHIO: Hi. This is Teresa Buracchio with Office of Neuroscience. I just

wanted to make a general comment, not specific to this discussion. I've heard some comments during our discussions about references to outside reports of potential misconduct in the studies, and I just want to note that although we are aware of those reports, we consider them to be unverified at this point until we do our own inspections. So the discussions and voting should be based on what is contained within our briefing documents, as well as what you may have heard during the open public hearing is also fair, but it should be limited to that data.

One other point I just want to make is that I've heard diversity raised a number of times as comments of concern with the data set, and I will note that we do often certainly encourage diversity in clinical trials, but currently it's not really an issue we would consider for whether a drug would be approved or not. It is something we would describe in labeling unless there was some specific reason, physiologic reason, to think the drug would act differently based on race, or ethnicity, or

gender. It's not something that we would necessarily weigh into an approval, but it would be something we would describe in product labeling.

DR. JONIAK-GRANT: Could I ask a question about that?

DR. NARENDRAN: Go ahead.

DR. JONIAK-GRANT: With the diversity piece, there are studies that have been out -- and I mentioned it earlier, the Frontiers in Psychiatry -- that does suggest that some of the benefits that we see with MDMA and others disappear for BIPOC individuals. So I feel like in this case it would still apply versus it just being, well, it's not required.

DR. BURACCHIO: It would be something that we would consider, and we would need to understand the thinking, or basis, or rationale for why you might expect to see differences. It would be considered as part of our review, but it typically wouldn't necessarily stop the approval of a drug if it was otherwise approvable.

DR. NARENDRAN: Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA, VA. So two points regarding this. First, I've raised before about, potentially, patients being coerced, not only I think in the acute period, but potentially in the sub-acute period afterwards. In the sponsor's brief -- I can't remember which page it was on -- they cite a paper talking about the brain plasticity effects and this openness to new experiences actually persists beyond the acute physiological effects of MDMA. I didn't have a chance to read that, but I think that's actually been talked about in the literature.

So with potential benefit, all those things sound good but, again, it potentially opens people up to coercion or manipulation. So I think, again, the agency being open to the fact that adverse events associated with MDMA should be recorded, should be monitored, in potentially the weeks, or even months, after administration.

The second point -- and I'm going to take a little bit of latitude on this because it's not directly addressing this -- is this idea of the

treatment as a whole. We're talking about midomafetamine, we're talking about the psychotherapy, but everything that goes along with it, and my understanding from the clinical trials is that patients were titrated off psychiatric medications. This is not something that we've discussed but, potentially -- and again, I don't know what the sponsor's position on this will be if it is approved -- with their training, are they going to recommend that patients be titrated off of their SSRIs?

I know in the trials, not just for midomafetamine, but in in many psychedelic trials, that has been a significant friction point, trying to get these patients off medications safely. And I don't think -- and correct me if I'm wrong -- that the agency recorded those or considered adverse events during those down-titrations as related to the drug because the patients did not receive drug yet. They had to be titrated off the meds before they were started on their first dose of medication.

So again, it's probably not within the direct purview of the FDA because you haven't been exposed to the drug, but if the sponsor is going to require, or at least highly suggest, patients come off medication, then I think it's fair game that anything untoward that occurs during that period be associated with the treatment package.

I know there's been talk about a, quote/unquote, "theoretical serotonin syndrome risk" with SSRIs plus midomafetamine but, actually, my understanding of the literature, two recent reviews -- Chris Opfer [ph], and then also my colleagues Dr. Price and Dr. DeBonis over at UCLA -- suggest that there's probably not a serotonin syndrome risk, and in fact, the likelihood for serotonin syndrome is actually probably lower if you have concomitant SSRI plus midomafetamine, at least in the acute period. And I believe they're citing trials where patients are on these medications 3 days, 5 days, maybe even a week. The pharmacodynamics suggest that the SSRIs will actually compete with your serotonin

transporter and displace the midomafetamine, so you're actually getting less serotonin release into the synaptic space.

The issue is that you get less of a subjective experience with the midomafetamine but, again, we don't know, and that's why I asked the question a little bit earlier, is there an association with that acute subjective effect and the outcomes, and, unfortunately, that data wasn't collected. But from a safety standpoint, there doesn't seem to be a safety issue. There was a theoretical blunting of the efficacy; that I would buy.

But again, if this is going to be paired very closely with this qualified healthcare provider training, I would be concerned if there was a strong message or recommendation to titrate folks off medications before treatment with midomafetamine because, again, as we know from other psychedelic trials, a lot of patients decompensate. So I don't know if providers -- well, I think providers would be much

more comfortable for a subset of patients if they knew they could administer midomafetamine without titrating their patients off some of the psychiatric meds that, even though aren't working great, are preventing the bottom from falling out. Thank you.

DR. NARENDRAN: Thank you.

Dr. Rebo?

DR. REBO: Elizabeth Rebo, Kaiser Permanente. In regards to question 3, when we were talking earlier in regards to proposed REMS, and it was talking about how it was studied for an extended period with overnight stays after most medication sessions, I think what I would want to see, if this were to be approved, is to have very strict guardrails around what that looks like.

Are we going to require overnight stays? Are we not? If we're not, what is the criteria for assessing the patient and verifying that they're ok? If we do see things like elevated heart rate and blood pressure, how long does it get back to, quote/unquote, "normal" before we release them? So

just having some very tight parameters around that; and then, of course, obviously, not letting the patient drive home and having an adult there, and signing some type of consent to release the organization of being a liability should they make a choice to drive after they get home or something like that. Thank you.

DR. NARENDRAN: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi, Georgetown. Having worked in the emergency department for quite some time, I've seen my fair share of intoxicated patients, including those who have taken ecstasy and molly. So one of my concerns here is they mentioned having two providers, one licensed and one maybe not, but I think another thing that we really need to have in place, in some capacity, is really ancillary staff, particularly if the patient is going to be there for a long period of time, and setting up things, for example, fall risks, elopement risks, when people are intoxicated. So a lot of the structural things aren't just providers or licensed there to

oversee it.

Then one of the other things, in emergency medicine, workplace violence is a real thing. What guards are we going to put in place, as far as a protocol for somebody who is acutely agitated, who becomes a risk to themselves and to staff in the interim, not just to keep the patient safe but also the staff as well? This hasn't really been brought up. That's all I have to say. Thank you.

DR. NARENDRAN: Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Thank you. Jess Fiedorowicz, University of Ottawa. I think there's risk for impairment with this medication. The REMS captures that in discussion of the timeline for monitoring. I think it will be important to be really clear in discussion of that. There are some components of the psychotherapy that also seem riskier in the setting of impairment, and we saw some examples of that.

Dr. Holtzheimer discussed how we usually look at adjunctive therapies when added to some standard of care. In this case, this psychotherapy

is experimental, and I think there were concerns about that that got raised by discussion of study design and might have motivated some of the discussion of a 2-by-2 factorial. But what we're looking at here is really comparing a medication to no medication in the setting of psychotherapy, and that that is the question of interest, although there were concerns that were raised in our discussion about whether there is a differential quality of the psychotherapy, based on the potential for therapist unblinding. Thanks.

DR. NARENDRAN: Dr. Hertig?

DR. HERTIG: John Hertig. I think we have, at some length, discussed there is a potential for impairment, as well as harm associated with this medication or this therapy. The only point I'd like to just echo is one that I believe was originally mentioned by Dr. Dunn with regards to the licensure status of those in the therapy room, and I would be supportive of two licensed individuals being in that therapy room just to ensure there are checks and balances on that

authority gradient. Thank you.

DR. NARENDRAN: Okay. We don't have anybody else who's there to add to, so I'll try to summarize this. I heard that there could be risk for coercion, manipulation, which could last even longer, beyond the duration, up to even weeks and months, so a REMS would have to capture those kinds of risks. I also heard concerns about the down-titration of active other psychotropic medications they might be on. That could be a concern and add to impairment risks. I heard that maybe an overnight stay could be better.

There should be more clear-cut criteria for heart rate, blood pressure, when the patients can go, and who they can go with. We also have to think in terms of the fall risks and elopement risks. The psychotherapy that's being performed during that time is in itself a risk. We also have to think about potentially the risks that the other people, the workplace staff and people manning the program, could be at risk for, and also put in some safeguards for that.

That summarizes the discussion. We'll move to question number 4.

Question number 4 is our last discussion. Discuss whether the proposed risk mitigation is sufficient to mitigate serious harm resulting from patient impairment. Include any additional safety monitoring conditions needed for the safe administration and monitoring of midomafetamine if approved for PTSD.

Any questions about the question? Yes, Dr. Fiedorowicz?

DR. FIEDOROWICZ: I just want a quick comment. I think 3 and 4 are blurred together, and my response to 3 is probably more appropriate for 4.

DR. NARENDRAN: So I can just copy and paste it, like ChatGPT does.

(Laughter.)

DR. NARENDRAN: Anybody want to volunteer to go first?

Dr. Dunn?

DR DUNN: Walter Dunn, UCLA, Greater Los

Angeles VA. This was an issue that was raised earlier regarding the two therapists in the room. Again, as my colleague, Dr. Hertig, just mentioned, I'm a big proponent to having two licensed therapists. I don't really see a reason why one individual would be unlicensed; however, if you decide to go through that route, and consistent with what the sponsor mentioned about having someone in training, I think it should be made clear that this person should be in training and is actually working towards licensure. Again, my concern with some of these for-profit organizations is that they would interpret that to fit their own agenda, again, using the lowest resources available to maximize profit.

As I mentioned before, I don't know if a REMS can do this, and perhaps the sponsor would do this in their training, and as they mentioned, this is something they're considering. Really examining the dynamic or the power differential between the two therapists in the room, my understanding of this requirement for two therapists is really for

safety. Again, that failed, unfortunately, very visibly in the phase 2 trials, and I can't help but think that that particular relationship between the two therapists played a role in that.

So if you have one therapist who's senior, as my colleague mentioned, and therapist who's a younger trainee, perhaps the younger trainee would be afraid to speak up, or if they did, their concerns would be dismissed. And I think that can happen, again, in a variety of situations, whether it be a fiduciary relationship, or what if one of the therapists is the owner of the clinic, and their employee is the other person in the room?

I'm reminded of a situation back in medical school where a colleague of mine was an aspiring orthopedic surgeon and her father was an orthopedic surgeon. I said, "Oh, that's really great. Do you get to go into the surgeries with him and watch?" And she tells me that, actually, he doesn't allow any family members to be in the room because if, heaven forbid, the family member had a medical emergency, his attention would be distracted, and

his focus should be solely on the patient. So if the the two therapists are in some type of, again, fiduciary or a personal relationship where that comes into conflict for the patient's safety, then I think that's a problem.

You can imagine another situation where, again, no such relationship exists, but -- again, if this is approved -- after working together for years and years and years, they become personal friends, then perhaps there would be a conflict, and one of the individuals may be reluctant to intervene or report their colleague to the medical board. So again, my understanding of the therapy is that the co-therapist, if they get along well, that actually improves the quality of the therapy but, again, I could see it potentially interfering with the role of being monitors for each other, essentially. Thank you.

DR. NARENDRAN: Dr. Rebo?

DR. REBO: Elizabeth Rebo, Kaiser Permanente. I brought this up when we were doing the presentations earlier, but it will answer

question 4 for me. I think because we still don't have the monitoring and the healthcare setting requirements fully baked, it's hard to say yes to this question because that hasn't been decided yet. So I would have to say no, based on the information that was provided today.

DR. NARENDRAN: Dr. Barone, who's virtual.

DR. BARONE: Hi. Liz Barone, again, VA Maryland Health Care System, and a couple of things that would be important I think. One would be really strict training, certification of the therapists, potentially by an outside group, organization, that's not connected to the sponsor, and then ongoing monitoring of the therapy sessions. I can't even imagine what that would look like, maybe recording all of the sessions and then submitting it to an outside group or something like that.

That would be probably my biggest concern as far as risk mitigation, and also providing really good medical training to the therapist. As somebody with no medical training, if I were in a

room with a patient who was demonstrating cardiovascular risks, but they're asymptomatic, like somebody was talking about earlier, I'm not sure I would know, and I'm not sure that I would be able to detect that and get them to the care that they would need. So I think that would be super important.

The last thing is something that's already been touched on, but having two licensed providers in the room. I do a lot of training for psychology interns and postdoctoral fellows, and in critical settings, really, training should not be used as staff, so there should always be two licensed clinical providers in the room. And then if a trainee is in the environment, and they're going to be learning the training or the therapy, they're the third person in the room. They're not there to be a true co-facilitator. They're there in a learning role. They're not really supposed to be functioning at the level of staff.

There's a huge power differential, as people already mentioned, so the idea that a trainee would

make a report against a supervisor when they are dependent on that supervisor for a positive evaluation is I think a little bit too idealistic to think that would happen in all situations. Thank you.

DR. NARENDRAN: Dr. Canuso?

DR. CANUSO: Carla Canuso, industry rep. I think without full characterization of the duration of impairment, it's hard to comment on the adequacy of the proposed REMS, but I would certainly recommend as part of that to include more assessment on the duration of those events and put some parameters around what stable looks like prior to discharge.

DR. NARENDRAN: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Just some comments on the REMS, we've talked about the two licenses; that's been well covered. Talking about being on site, I think for me I'd really want proximity to be figured into this, what does it mean to be on site and have that be pretty narrow. There's lot of discussion about lab information

that's needed, so I think the collection of labs is necessary. I do like looking at certain healthcare settings. I think that's important and having training of therapists outside of the sponsor, and as was mentioned, too, to have medical training, especially to people who are psychologists or other areas where they might not be as aware of what to look for with some of the risks.

One thing I do want to point out is there's been some talk about doing surveillance, recording the sessions, having the tapes, and having these things. I'm a sociologist, and my background is in social control, and surveillance is great, but the reality of it is, surveillance rarely ever gets looked at. It is something that gets filed away, and if there's a problem later that's brought up, perhaps six years later, maybe someone can go back and find it.

But that's one thing, so if there's anything in a REMS that's talking about doing surveillance, there needs to be very explicit directions in terms of what are we going to do with that surveilled

information, so it doesn't just end up in a box somewhere. I think that's a really important point that I want to make.

Then finally, I think the idea of having a registry is good. I would also want there to be a clear way for participants to report adverse events outside of the institution and outside of their treating therapists, and have that be part of any type of consent that they would go through; so they have this outside party that they can reach out to and report things to.

I think that's something that a lot of patients who have been in healthcare for a long time, and they've had a lot of experiences, perhaps medical trauma, where they've reported issues, and they'll say, "Well, it's not in the label, so it must not be caused by this drug. I think that's just you." So having this other way for people to get information out there would be really useful.

DR. NARENDRAN: Ms. Witczak?

MS. WITCZAK: Kim Witczak, consumer rep, and you actually took one of my big things away --

DR. CANUSO: Sorry.

MS. WITCZAK: -- and that is, part of the element in the informed consent is having a clear pathway for reporting, whether it's reporting to the FDA through MedWatch, the companies. I've been around drug safety issues for a long time, and I hear from harmed patients, and the reality is people report, nothing gets done, and it's probably one of the major complaints from patients, especially the harmed community, is no one listens. So is there a clear pathway? What is it? Is it independent?

Then also, when I just heard that we're not going to investigate something because it wasn't part of the application, that makes me a little bit nervous for the patient who might experience harm. If we know that we're going into it with something that might not be there, that makes me a little bit uncomfortable because I know what happens in the real world with reporting. So that was one thing.

Then, monitoring of somehow, whether video -- and I'm not the one that doesn't go

through it for boxes, but maybe there's some kind of systematic way, periodically, because I know that these sessions were all videotaped for this application. Maybe there's some independent group that could go through and periodically check as a way to see if it's all being done. I know that puts a lot of burden, and I get it, because it wasn't as simple as just the drug and the therapy. Then of course, you guys heard many times, licensed practitioners or the licensed therapists in there because of, again, power dynamics, which is a real thing for patients and consumers. Thank you.

DR. NARENDRAN: Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA, VA, a question and then a comment, and a question actually from my colleague, Dr. Canuso. This idea of the REMS, and safety, and access, many of the comments today have recommended increased safety guidelines and parameters, and I think we have to be mindful that, unfortunately, that also impacts access. And for someone who was involved in a recent approval of a treatment that had a significant REMS component to

it, do you have any sense of how much that REMS impacted the rollout of the drug and patients' accessibility to that drug?

DR. CANUSO: Not quantified, and I think there were many other confounders because there were other access issues like insurance coverage at the time, but COVID was a big factor in limiting access because of the REMS and patients needing to come into a doctor's office. But now that we're past that, drug is getting to patients, and the REMS is similar to what is being proposed, and it's implementable.

DR. DUNN: Okay. Great. Again, I just wanted to raise the issue that while we certainly want this to be safer for patients, we have to recognize that all these recommendations, two licensed therapists, are going to reduce the number of therapists who are available to do this and reduce access and availability.

I was encouraged to hear from the agency that the REMS will be an ongoing discussion and dynamic and, again, if approved and if a REMS is

implemented, that this will not be the only iteration upon additional real-world data; that they can revise it either to be more restrictive or less restrictive. I think many of the REMS programs for some of our older drugs have been static for a very long time, but I think, again, responding to real-world data, we should be willing and able to make revisions when the evidence is compelling that they should be made less restrictive or more restrictive.

DR. NARENDRAN: Alright.

With that, we'll try to summarize this discussion. I think we heard a fair amount. I heard that the risks are not fully characterized, so the answer to the question might be no. What needs to be added, I heard two licensed therapists, multiple people, and I quote that, "the power dynamic between the two licensed therapists is also very important because that's where harm can happen."

I heard training by an independent outside group as opposed to the sponsor would be a good

idea. Providing also good medical training so people are aware of the cardiovascular risks and to be aware of what could potentially medically go wrong for the therapist could be very helpful. The proximity of the medical person to be on site was a big concern that was raised as well, and adding more lab information, EKG, and vitals monitoring.

Monitoring and video surveillance is also mentioned, but it's surveillance; somebody has to pursue the surveillance and make sure it's being done, it's looked at, and that potentially could be done by an independent group or audited periodically, and that could perhaps address that. I also heard that there should be an independent outside track for patients to complain and not through the treatment provider or the program that's been administering the drug because they may be more likely to discount it. Lastly, I heard the REMS should not limit the access for patient care, so that summarizes that.

With that, we'll move to question 5, which is a voting question. Do the available data show

that drug is effective in patients with posttraumatic stress disorder?

Are there any questions about the voting question?

(No response.)

DR. NARENDRAN: No questions about the voting question?

MS. WITCZAK: I have a question. Should it really say the name of the drug plus therapy or is it just the drug? Because to me, there's the MDMA, but it has to be the application, right? It's the company application?

DR. FARCHIONE: Yes. The context that we're reviewing is, in both treatment arms, there was psychotherapy present.

MS. WITCZAK: But should we put psychotherapy as part of that? Does that need to be part of it?

DR. FARCHIONE: The proposed indication is midomafetamine with psychological intervention.

MS. WITCZAK: Yes. Thanks.

DR. NARENDRAN: We'll be using an electronic

voting system for this meeting, so once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed. The virtual people will be voting through e-mail to the DFO.

Question number 5, do the available data show that the drug is effective in patients with posttraumatic stress disorder? Vote.

(Voting.)

DR. FRIMPONG: There are 2 yeses and 9 noes, no abstentions.

DR. NARENDRAN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted into the record. We'll start with Dr. Dunn.

DR. DUNN: Walter Dunn, UCLA Greater Los Angeles, VA. My vote was yes. I think there are concerns about the functional unblinding in addition to the expectation bias, potentially reducing my confidence in the effect sizes that were reported; however, I can't overlook the fact that the effect sizes were fairly large, and I think worst case scenario would be down to something like 0.3, 0.4.

But per Dr. Buracchio's guidance earlier, and really not taking into consideration the possibility for misconduct, I think if that is fully fleshed out, and if that really changes the data, based off of some type of sensitivity

analysis where sites that were identified to have engaged in misconduct were removed from the efficacy analysis, then I think we should see that data. But again, assuming that no misconduct occurred, but accepting that there was functional blinding and most likely expectational bias, I think that the defect sizes are still large enough that this treatment, drug plus psychotherapy, can be effective for patients with posttraumatic stress disorder. Thank you.

DR. NARENDRAN: Raj Narendran, and I voted no. I felt the functional unblinding, lack of management of expectation bias, and also the selection bias of people, 40 percent of them had used MDMA. So not without accounting for what their expectation was, and somehow incorporating that into some kind of statistical model, I think it's meaningless. I just feel very convinced that I had to vote no.

DR. FIEDOROWICZ: Jess Fiedorowicz. I voted no, and nothing to add to the discussion.

DR. IYENGAR: Satish Iyengar. I also voted

no for similar reasons that Raj mentioned. It actually felt strange to vote no when the p-value started with three zeros, but there were just too many problems with it, and unless you have a model for the biases, it's really hard to make a judgment about whether it's accounted for.

MS. WITCZAK: Kim Witczak, consumer rep. I voted no. I do think there is potential for this, but based on selection bias, functional unblinding, it didn't feel right, and the potential for some misconduct and manipulating the trial results.

MS. JONIAK-GRANT: Elizabeth Joniak-Grant. I voted no. This was a difficult decision for me. I think that some of the data was promising, but given the 40 percent that had previously used MDMA, limited information about recruitment and recruitment coming through referrals, I really wonder how much that impacted the efficacy. Durability not being assessed multiple times and a one-shot deal was another issue for me, and I am concerned with the lack of diversity in the sample and what that would mean for the general

population.

DR. HERTIG: John Hertig. I'm the second of the two that voted yes. Along with Dr. Dunn, I do share his assessment, and in the interest of time don't have much additional to share. I do believe that the therapy holds clinical promise. Thank you.

DR. AMIRSHAHI: Maryann Amirshahi. I voted no. Similar to many of my colleagues, I felt that the large positive effect was denuded by the significant confounders. Although I do believe that there was a signal, it just needs to be better studied. Additionally, the population considerations that we discussed really limit the generalizability to the larger PTSD population; and then also, the inability to tease out the relative effect of the variable therapy provided. Thank you.

DR. REBO: Elizabeth Rebo. I voted no, very similar to concerns that Maryann just articulated.

DR. NARENDRAN: I do want to give our virtual members an opportunity?

Dr. Barone?

DR. BARONE: Hi. Melissa Barone. I voted no. In the interest of time, my concerns have already been noted by the committee.

DR. NARENDRAN: Dr. Holtzheimer?

DR. HOLTZHEIMER: Paul Holtzheimer, National Center for PTSD. I also voted no for reasons previously stated.

DR. NARENDRAN: We'll now proceed to question 6, which is another voting question, and same instructions. We'll be using the electronic voting system. Once we begin the vote, the buttons will start flashing, and will continue to flash even after you entered the vote. Please press the button firmly that corresponds to your vote. The DFO will read the vote from the screen into the record, and then we'll go around the room, and each individual who voted will state their name and why they voted, if they wish to.

Question number 6, do the benefits of midomafetamine with FDA's proposed risk evaluation and mitigation strategy, REMS, outweigh its risks

for the treatment of patients with PTSD?

Any questions about the question?

(No response.)

DR. NARENDRAN: No question about the question, and we can vote.

(Vote.)

DR. FRIMPONG: Bear with us. We're still waiting for one more vote from one of our virtual panel members.

(Pause.)

DR. FRIMPONG: For our question, there is 1 vote for yes and 10 votes for no, and no abstentions.

DR. NARENDRAN: We'll start from this side of the table.

Dr. Rebo?

DR. REBO: Elizabeth Rebo. I said no, primarily because there are too many missing parameters around it for me to feel comfortable saying yes.

DR. AMIRSHAHI: Maryann Amirshahi. I also said no for the fact that there was a lot of

missing safety data, and the efficacy data is somewhat equivocal in my mind. Thank you.

DR. HERTIG: John Hertig. I also said no. Although I did feel there was some effectiveness here, I don't feel like the risks, the missing data, the gaps, the unknowns outweigh that benefit, so I voted no. Thank you.

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I voted no. Sorry. It's been a long day. I think we're still trying to understand the risks and echoing what others have said before. So for me, it's a no.

MS. WITCZAK: Kim Witczak, consumer rep. I voted no, and because we are in this new territory, I want to commend both the FDA and the sponsor for bringing this forward. I don't think we're quite there yet, but I think the conversation's there, and I'm looking forward to seeing where it can go. But for the reasons that we've proceeded to talk about, I voted no.

DR. IYENGAR: Satish Iyengar from Pittsburgh. I also voted no for pretty much the

same reasons as my colleagues.

DR. FIEDOROWICZ: Jess Fiedorowicz. I voted no.

DR. NARENDRAN: Raj Narendran, and I voted no.

DR. DUNN: Walter Dunn. I voted yes; not the first time I've been on the short end of a vote, and perhaps this requires a little bit of commentary. I wish we had a Likert scale in addition to our yes and no votes because I voted yes, however low on my confidence about the risk-benefit.

Two things about it; number one, I think the greatest strength of the treatment is also its greatest liability, and that's the therapists in the room, the psychotherapy, and, unfortunately, that sounds like it's out of the direct purview of the agency. Number two, as was mentioned previously, the REMS is still something that the sponsor is having conversations with the agency, so we actually don't know what that REMS looks like; however, based off of what's been presented thus

far, it's probably 75 percent of the way there. You're definitely on the right track. I think a tweak here and there can address some the safety concerns we've brought up.

So those are some of the things that would shift me towards the no vote. Ultimately, I voted yes because I'm putting on my clinician hat, and as has been stated before, we are in dire need of new treatments for PTSD. And I'm especially sympathetic to the stories of our veterans that were here during the public commentary. Working in the VA, as a former service member myself, I have colleagues who deployed and have PTSD, and this has the potential to make a difference.

Now, that's not without its risks, but as I like to tell all my trainees, there's no free lunch in medicine, and what has the potential for benefit has the potential for harm. So again, as has been mentioned by the agency multiple times, there's no such thing as a, quote/unquote, "safe treatment." It's all about the risk-benefit profile. So I think as the REMS evolves, I think it can be made a

safer treatment in the right clinical context, in the right healthcare settings, so I think that advantage can be gained with the right guardrails in place. Thank you.

DR. NARENDRAN: We'll go to our virtual panel members.

Dr. Holtzheimer?

DR. HOLTZHEIMER: Paul Holtzheimer, National Center for PTSD. I voted no, largely for reasons stated. I'll just comment that I absolutely agree that we need new and better treatments for PTSD, especially in the somatic treatment space; however, I also note that premature introduction of a treatment can actually stifle development, and stifle implementation, and lead to premature adoption of treatments that are either not completely known to be safe, not fully effective, or not being used at their optimal efficacy. I think this is a really exciting treatment. I'm really encouraged by the results to date, but I feel that both from an efficacy and a safety standpoint, it is still premature.

DR. NARENDRAN: Dr. Barone?

DR. BARONE: Melissa Barone. I voted no. I think that this treatment is incredibly promising and has a lot of potential to help a lot of patients. I just think that there needs to be more research done to address some of the questions and concerns that have been brought up today. Thank you.

DR. NARENDRAN: Okay. I do want to thank the sponsor for really trying to bring this novel therapeutic and putting all the effort to get this in front of the agency. I do want to thank the agency for the very difficult problems you guys deal with and have to contend with psychedelics as a therapeutic.

Are there any closing comments from the agency?

DR. FARCHIONE: I just want to echo the thanks to the applicant and to the committee, and especially to the folks who participated in the open public hearing today for sharing their stories. Thank you.

Adjournment

DR. NARENDRAN: Thank you. With that, we will now adjourn the meeting.

(Whereupon, at 5:43 p.m., the meeting was adjourned.)