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SPEAKERS

Amy Emerson, Dr. Bera Azhar Klosinski

D **Dr. Bera Azhar Klosinski** 00:00

Hello, I'm Bera Yazar Klosinski PhD, and I'm the Chief Scientific Officer of the maps public benefit corporation. And I've worked at the maps group of companies for the last 11 and a half years on all the clinical trials that maps has sponsored. And I'm excited to tell you more about our MDMA assisted therapy research today, along with my co presenter, Amy Emerson.

A **Amy Emerson** 00:30

Hi, I'm Amy, and I'm the CEO of the maps public benefit corporation. I've been working with maps for a long time now since 2003. And my background is in really in drug development, I've worked in the vaccine field for quite some time before this, and my degree was in genetics and cell biology. And I feel really lucky to have spent much of my time working now at maps and at maps PBC, our mission of bringing MDMA for PTSD into the medical system. And I'm just going to point out just briefly, on the next slide that we have a disclaimer here for the integrative psychiatry Institute. And I want to particularly draw attention to a few bullet points at the bottom that MDMA is still an investigational product. It has not yet been approved by any regulatory authority for prescription use, and it does not work for everyone and there are risks. On the next slide, just briefly, note that this is copyrighted material for the integrative psychiatry Institute. And I'll turn it over

to Barrow to give you some of our learning objectives for today.

D

Dr. Bera Azhar Klosinski 01:43

So today, we're going to review the current research initiatives involving MDMA assisted therapy that are sponsored by maps. And we're going to reflect on some of the available results from phase two and phase three trials and talk about the general study protocol of MDMA assisted therapy that's being developed for approval by regulatory authorities.

A

Amy Emerson 02:07

So I'm gonna start with a little bit of the history of MDMA. So there's quite a long history of research with MDMA. And some of this history was actually quite helpful for us in building our program that we're going to tell you about today. MDMA was first synthesized in 1912, and patented by Merck. For the most part, it was shelved, it was the minimal experimentation done by Merck in the end in the 50s. And then, some now declassified research done by the US Army that I'm sure you can look up and find some information on. But I'm going to start into the part that's more relevant to us as when Sasha Shogun independently resynthesize, MD MDMA in the mid 70s. And he trusted the drug tested the drug on himself, and he recognized that it had properties that were potentially helpful for therapeutic use, he noticed that it had an ability to allow for increased access to emotionally intense material. So Sasha then gave the MDMA to his psychologist friend Leo Zeff otherwise known as the secret Chief, to try it in therapy with his clients. And so from then until about 1984, MDMA was used as an adjunct to therapy for many therapists, approximately 500,000 doses were used in therapeutic and personal growth settings prior to MDB, MDMA being scheduled and placed on the schedule one list of controlled substances, which happened in 1985. And that is where MDMA remains today, but hopefully not for too much longer. The scheduling happened because not because of the therapeutic use, but because it was a response to widespread recreational use, and that scheduling abruptly ended all medical and research use of MDMA. So prior to that, rescheduling, Rick Doblin who started maps had one kilogram of MDMA synthesized with the intent of having it available for medical research because he could see what was about to happen. And in 1986, he started maps, which began the long journey of starting FDA approved research for MDMA assisted therapy. From there, it took another 10 years before that research could actually enter a phase one study. But during that time, there was a lot of government research on MDMA to assess the risks of the drug. This was actually quite helpful to maps, as we were able to use this data to create the first investigator brochure for MDMA without having to do the research ourselves. So that available research also allowed maps to move fairly quickly from just one phase one study in healthy adults that was done by Charlie Grove in 1996, into a phase two program

with PTSD. The first clinical trial was actually done in 2000, and it was done in Spain and conducted with Marcello telara, who we still work with today. And unfortunately, that study only was able to enroll a few people before it was shut down for political reasons. So then the US IND, so that we could start research in the US was approved in 2001. However, it still took a number of years before we actually were able to get to treating a patient, four years in total, from that time of the ind until the first protocol that was done with Michael Hofer, was fully approved by the FDA, IRB and DEA, and in 2004, the first participant was treated. So from there, the US program was underway, and it took 12 years to do another six studies. And those were completed in the US, Canada and Israel. And that allowed us to reach what you call an end of phase two meeting with FDA in 2016. Things sped up a little bit more from there and the phase two data based on that phase two data and various scientific publications. This actually led to in 2017, getting breakthrough therapy designation with FDA. And from there, the phase three program was approved by FDA and started in 2018, and we received positive scientific advice from the European Medicines Agency that that year as well. And so now we're in the point of the phase three program in 2020, or pivotal phase three. So our first phase three study was completed, and we're going to share those results with you today. And currently, we're in the process of making more history with our second phase three, and our European program that started just recently with the open label lead into phase three. So I'm going to turn it over to Bera for a little more information on how MDMA works.

D Dr. Bera Azhar Klosinski 06:31

So MDMA is a really interesting compound, it has multiple mechanisms of action, and we feel that this is particularly why it can be so powerful as an adjunct to psychotherapy. So the figure that I'm showing you here is a close up on a neuron, which our brain cells that we know some things about, and in terms of MDMA is mechanism of action. So the electrical signal comes from the axon, and then molecules and neurotransmitters that are present in the presynaptic part of the neuron, facilitate information transfer over this gap, which is called the synapse, into the postsynaptic part of the neuron. So this is how electrical signals are transmitted in your brain, and it leads to all sorts of effects that you may be familiar with, such as emotions and feelings and thoughts and memories. But really, it's all about these little building blocks here that are shown on this figure. And MDMA has impacts on three kinds of neurotransmitters, the primary effects are on serotonin secondary effects or on norepinephrine, and tertiary effects are on dopamine. And this relationship in terms of the effects are species dependent, so you might see different things in mice happening from rats and humans, however, animal models are a strong basis for what we know about MDMA today. In addition to releasing these mono amine neurotransmitters through either inhibiting v mat two, which is a pump that, you know, promotes filling the circles in the presynaptic membrane. MDMA also inhibits mono

amine oxidase A, which breaks down these neurotransmitters. So in summary, MDMA turns on all the faucets in your brain and results in these neurotransmitters. triggering signaling cascades, that further downstream also release neuro hormones such as oxytocin, cortisol, arginine, vasopressin, prolactin, and acth. And so, with all of this massive action going on, people experience subjectively the feelings of MDMA, which are pro social effects, typically. And also, MDMA functions as a nonspecific amplifier of whatever emotions or memories are present already in the body. So let's talk a little bit about why about PTSD specifically. So post traumatic stress disorder is inherently a difficulty and extinguishing fear. And what I'm showing you here are two subtypes of post traumatic stress disorder. One is the non dissociative subtype. So in this instance, there's less signaling in the prefrontal cortex. So kind of thoughts and logic are controlled by this part of the brain. And there's more signaling typically In the amygdala, which governs the fight or flight response and fear responses, there's also typically less signaling in the hippocampus, which controls your memories. In contrast to this and the dissociative subtype of PTSD, there's often more signaling in the prefrontal cortex and the thoughts involved with those. There's often a reduced signaling or emotional numbing going on in the amygdala, and also reduced signaling in the hippocampus, so less access to memories. So the hippocampal effects are consistent between the two types of PTSD. And PTSD is characterized by frequent re experiencing of the traumatic event. There's often flashbacks and intrusive memories and nightmares. There's also avoidance of trauma related thoughts and situations because it's triggering and emotionally very challenging. There's often negative beliefs about oneself and the situation and the feelings involved. And typically, in the non dissociative subtype, hyper arousal and reactivity, which, you know, community members or family members may experience as a perceived irritability and hyper vigilance of the individual suffering from their PTSD symptoms. And so the symptoms if they last for longer than a month, are considered to satisfy diagnostic criteria for PTSD. But what we see in actuality is that PTSD is very often a chronic condition. And many of the participants in our studies have had PTSD for years, often since childhood. And of course, these symptoms, understandably cause a lot of emotional distress and functional impairment. So it's really difficult to go through daily life. So let's talk a little bit about why MDMA makes sense to study in order to overcome PTSD. So brain imaging studies and animal studies have shown that, in rodents, MDMA is able to promote fear extinction, meaning it can end the fear in mice. And also we have seen in rats study that MDMA can modify fear memories during a reconsolidation and memories are typically generated and then consolidated in the brain so that they're stored long term. So if MDMA comes along, and these memories are brought to the surface, through an experimental model or or through therapy in humans, then if MDMA is present, it can modify how those memories are subsequently stored and reconsolidated. In addition, MDMA has been shown to trigger neuroplasticity, when administered in close in time, to an experiment where the rodents are, have to learn something in order to go through a

maze or something along those lines. And this neuroplasticity effect is really interesting, because, first off, it's very challenging to study this in people, which is why these studies are done in animals. But if MDMA could rewire the brain, essentially, then as seen in rodents, it can reopen critical periods and development were very triggering traumatic memories have been generated and stored and enable an opportunity for folks to reimagine what their traumatic traumatic event might be, in the context of therapy. So we have some unpublished data that suggests that the network level effects of MDMA in the brain are durable and lasting. So we have a study in 10 people who were veterans or first responders, that showed that the amygdala signaling goes down after two months after last exposure to MDMA. And similar to classical psychedelics, which are known to influence the default mode network in the brain, which controls kind of repeating thoughts cycles. MDMA also may have the ability to attenuate this activity in those repeated thought cycles. So it's lots of interesting stuff happening in brain research with MDMA, and Amy is going to tell you a little bit about what this might look like in the context. Extra therapy.

A Amy Emerson 15:02

There I think one of the things that's interesting about what you're saying about memory reconsolidation rewiring the brain is I think about watching some of the videos and hearing some of the quotes from the participants in the study. And I remember one specifically of somebody saying about like PTSD, change the wiring of my brain and MDMA, rewired it back. Right. So it's like interesting that in metaphor, people's experience is of this brain plasticity and memory reconsolidation. And we hear different quotes like that at times that really made me think about the model that you just described. So yeah, let's think about how. So bear has told you about some of the PTSD symptoms, we told you a little about how MDMA looks. And so we have this model called where we could talk about a window of tolerance or an optimal arousal zone. So if you think about that, there's these two types of PTSD one is more towards a hyper arousal side and what is more tied towards a hypo arousal side. So the hyper arousal is a lot of emotional reactivity, anger, intrusive images, and disorganized thinking. The hypo arousal is numbing, lack of emotions, difficulty connecting, it's hard to leave the house hard to find any kind of motivation. And it's really hard to feel anything. And then both of those groups, you also get very poor sleep quality, nightmares, difficult relationships, lack of trust, poor quality of life, lack of empathy, of self empathy, and high rates of suicidal ideation and behavior. And then Barry told you a little bit about what is pts or what does MDMA do, and it's really the opposite of what PTSD does, you have enhanced mood and well being increased alertness, reduced fatigue, a sense of closeness to others and empathy, a heightened openness, this emotional communion, and it is a it's considered an empath region or an intact region. So if you kind of put these things together with, with

the models that he was talking about, and the way PTSD affects people, and the way MDMA does it, the MDMA we think is create creates this window of tolerance. It's like an optimal arousal zone. So if you're in that hyper arousal state, it brings you down into it. And if you're in the hypo arousal, it brings you up into it. And from this place, people can start to have reduced fear, increased trust, and start to process their traumatic memories. And so an important part of going to the next slide, important part of processing those memories is having a proper set and setting. So in our modality, the treatment sessions are completed up to three times and they're spaced three to five weeks apart. And there's preparation visits before. And there's integration visits after and follow up phone calls. But this setting setting is such an important part of therapy, as well as that timeline of like how the therapy takes place, you have to control it, you have to create a conducive physical and mental environment for the therapeutic processing and the fear extinction process to begin. So the visits are in done in a setting. This is a picture of one of our sites, I think it's at UCSF, and you can see it looks like a nice kind of living room type setting. All the patients are there with two therapists, and there's music that's used and there's eyeshades that are used, and then the MDMA is part of that set and setting right it is what is assisting the therapeutic process to happen. And it supports this, you know, this window of tolerance opening and the PTSD symptoms are reduced, your trust is increased. And your and people begin to process their traumatic memories. And we call our therapeutic approach, inner directed in that we support that patients to experience unexpressed, whatever is emerging in their awareness at the time. So this is quite different from other types of therapy. So that the therapy team Cold's this empathetic presence, they support the unfolding healing experience. And we allow the person's inner healing intelligence to emerge, the therapist follow along and support the participant in a way that meets them in their arising need. And in that moment. So during this process, there's also periods of talking and long periods of quiet, it looks different for each person. And that's what's special about this. And that is that allows it to be kind of customized to the person's experience, and what is arising for them at the time, and it looks very different for each patient. The next important part is integrated visits. And these are set up in a similar way with the same kind of setting setting and they're an important part to the overall treatment. It's a time when the participants are able to explore what the therapist their insights that they received during the treatment sessions and to help them begin integrating That information. So let's look next at the actual study design. So there's that's, that's the modality. And now that modality is set into a protocol right now, because this is still research. And we first started with a phase two program. And in that program, we had a few variations to design. If you remember from the history, we did about six phase two studies, each of them had some variations. So this is kind of an overall theme to what what the study designs look like, there were two eight hour treatment sessions using either MDMA, or a competitor. The competitor in some studies was MDMA, at a low dose, and in some It was a placebo. The those sessions are represented by the blue triangles that you

see on this chart. There were also 90 minute non drug therapy sessions, and those were approximately a week apart. And those are the green lines for integration. So the experimental sessions were three to five weeks apart, and the integration visits were after each of them as well as some phone calls to ensure that the safety and that of the participants during the study, our primary outcome for phase two was after the second session, so two to three months after the second treatment. And at that point, every person was unblinded. And our primary endpoint was measured by an independent rater. And then the participants when they were on blinded to treatment, if they were in the full dose group, they were able to go on and get the third experimental session, that's the third blue triangle there. And if they were in, and then they would have a cap and the other assessment, so they had their assessments after two sessions, and after three sessions, and then the people in the comparator group, were able to go back and do what we call stage two, and basically complete the whole study again, with three folders sessions of MDMA. And then everybody had a one year or longer follow up after that. And there's going to share a little bit more about the doses and the results from this.

D Dr. Bera Azhar Klosinski 22:00

So we had some ideas going into this program about what kind of doses would be appropriate to test for MDMA. And this was largely informed by some of the historical therapeutic use that Amy described to you as part of the history of MDMA. So from publications as early as 1968, we had an idea of what the therapeutically active dose range was, and these doses informed the doses that we picked for the clinical trials. So we tested a range of lower doses of MDMA, from starting from inactive placebo through 40 milligrams of MDMA, as an initial dose, followed by one and a half to two hours later, a supplemental dose that's equivalent to half of the initial dose. So if it was 40 milligrams initial, the supplemental dose was 20 milligrams, and so the goal of testing these lower doses of MDMA was to try to optimize the blinding of the study. And we also measured the strength of the blind in the context of the phase two studies. The 75 milligram dose, we weren't quite sure, so we called that a medium dose initially, in the study that we tested that, we had a pretty good idea that 100 milligrams, and up would be therapeutically active based on the the 1968 publication on therapeutically active dose ranges. So what we found in our studies was that the 75 milligram through 125 milligram initial dose followed by a supplemental half dose was their reputedly active and this form the basis of the doses that we selected for the phase three studies in the end after these explorations. So what I'm showing you here is a pooled analysis of six phase two studies, and we put all the individual participant data together and pretended as if it was a single study. And this is only statistically considered okay to do under certain circumstances, so those circumstances are summarized on in the bullet points. We already knew that we had multiple studies that had demonstrated statistically significant results and had a large

effect size on their own. And so only under those conditions would it be appropriate to pool individual observations across multiple studies together. There is a risk of doing that, which is called The Simpsons paradox. So you can get different results if you put things together versus when you analyze them individually. So out of the five completed phase two trials, two of them were significant. And one study, the six was terminated early. This was our Canadian study. And at that point, all the other studies had been completed and we had to move into our into phase two meeting that Amy was telling you about earlier. So in MP one, this was the first proof of principle study, the sample was primarily female sexual trauma survivors. In MP eight, this was a three arm dose response study comparing 30 milligrams to 75 milligrams to 125 milligrams, and thus one was primarily in male veterans, but also included other first responders like firefighters and a police officer. So when we look at the pooled analysis, after looking at outcomes after two experimental sessions at the primary endpoint, we found a robust significant reduction in PTSD over the therapeutically active dose range. And this was measured with the clinician administered PTSD scale, which is a clinical interview, administered by blinded independent raters. In addition, we found that the pooled effect size as well as individual effect sizes from the studies were large, we were not sure if two sessions or three sessions would be the most appropriate to study in our phase three trial. So a subset of the participants who received an active dose, were given the option to continue on and receive a third session. And so about 51 people participated in that component of the study. And we found that reductions continued. So this all informed the phase three design that we ended up following for the subsequent studies. And Amy is going to tell you a bit about the individual level effectiveness data.

A Amy Emerson 26:59

Okay, so in this, so we didn't want to just look at p values, right, we want to look at also the symptoms of the PTSD. And we want to look to see if they are clinically significant, Lee reduced, and we want to look and see if people are losing their PTSD diagnosis. So we, in this pool data, on average people that had 18 years of PTSD before they entered the study. And in the control group, we saw 23% of people after treatment, and this is after two sessions no longer had PTSD. And this is kind of on par with some standard, the standard of care that you see some loss of diagnosis, and some people after treatment. But in the active dose group, we saw 54% of people no longer met the criteria after just two treatments. So this is pretty impressive, gave us a lot of hope for designing our phase three study. And then we also looked at, if you remember I talked about that people, we had to design where people did stage one and stage two. So that since this was after two doses, some people went on to research receive their third dose, or the control group went on to do the whole study again and have three doses. So at the exit, so after their final dose, no matter what group they were in, we also looked at this, and we saw that 82% of

people had had a treatment response. So that was a clinically significant drop in their PTSD symptoms. To go along with, I think it was a little bit more like 56% of people it had a loss of diagnosis at that point. And then we also wanted to look and see if if it lasted. So we did this long term follow up to look at durability. And what's impressive is that it does appear to be durable. So not only after, you know, are we seeing a big improvement after two or three doses. We saw one to six years later, that the people no longer meeting the criteria for PTSD had increased from 47% to 67%. And we also saw that the clinically significant improvement in symptom relief had been sustained. And all that 12% of the people meaning that 11 of 91 people had relapsed, so nine were due to additional stressors, that and for various reasons, and the other were just a return of symptoms where they didn't feel like there had been additional stressors that had created that. And it kind of makes sense if you think about what we're saying in the way that we're approaching the treatment between PTSD and that we're trying to get to the root of the problem. We're trying to get to the trauma, memory reconsolidation and brain plasticity, so people are feeling much better. You're not just treating the symptoms, and so their lives are improving significantly at the end of the study. But that means there's a lot of room for their lives to continue improving. So all those things that we said PTSD, Cause, like disconnection with family with self nightmares, all of these types of things. Those are better at the end of the study, but they continue to improve. And we think that's why we continue to see a loss of diagnosis. People also could go on to any other treatment that they wanted to. But remember that these were treatment resistant people, so most of them had tried all kinds of things ahead of time. So the difference is that they had the PTSD treatment this time, and some of them may have returned to some medications or to other types of therapy. But it's, but it's still very promising that the PTSD MDMA treatment was a breakthrough for their PTSD and their symptoms, more or decreased or they lost their diagnosis completely, and that was sustained.

D Dr. Bera Azhar Klosinski 30:42

So we had all this data, and it was we knew we had something really important for the patients who were suffering from PTSD and did not have many options for treatment. So we conducted a historical comparison of our data to the data from sertraline, paroxetine, or Paxil and Zoloft that are currently approved in the US and in other countries worldwide for treatment of PTSD, and on the basis of effect size, which is essentially kind of standardized way of comparing across studies. We found that we were able to show there was a pretty distinct difference between available PTSD medications and the pooled effect size that we had. In addition, there were some key differences in the tolerability of these treatments, so sertraline, and paroxetine, were both approved on the basis of 12 week studies considering our consisting of daily dosing. And with MDMA, we were able to achieve these results with two or three sessions and a significant amount of

psychotherapy. So with the amount of unmet medical need, that's, that's, unfortunately, the situation for PTSD patients. We made the case to FDA, that insufficiently treated PTSD is in fact, a serious and life threatening disorder. And that available medications were not sufficient and left a significant amount of unmet medical need. And on this basis, FDA agreed with our analysis and granted MDMA breakthrough therapy status. And with this breakthrough therapy status, we have the benefit from a regulatory perspective of getting additional help from FDA, and additional input from them on our overall program, and the design of the program, so that hopefully, one day we can get approval for FDA from FDA, and other regulatory agencies as well for the use of MDMA, and as an adjunct to therapy for treating PTSD. We also had found some secondary benefits that Amy was just mentioning, such as improvement and sleep quality, we found an increase in post traumatic growth, including positive changes and self perception and interpersonal relationships that correlated with these improvements and were durable, at least 12 months after treatment. We also found a durable reduction in alcohol use and an increase in openness. So all these are kind of secondary benefits that we feel reinforce the improvements that we're seeing in the context of PTSD and also improves our confidence that the PTSD findings are real. So of course, any drug has, has risks and side effects. And we primarily focus on testing MDMA, in the context of either low dose control MDMA studies, or, in comparison to the therapeutically active dose studies. So what we saw is a mix of adverse events that are often commonly seen in the PTSD patient. So they, they could be a mix of background events as well as effects of the drugs. So in the absence of inactive placebo control, it's it's a bit challenging to separate out what's a true safety signal, which is why we needed to do the phase three studies that we're going to tell you about next. So, of course, some of these effects are, you know, expected as as a result of of having MDMA. We also already knew based on prior publications, that MDMA is a sympathomimetic drugs, so it increases heart rate and blood pressure due to the multiple mechanisms of action that I had summarized earlier. So there's a transient increase in heart rate and blood pressure, there's the potential for psychological distress. And the therapy helps with buffering some of this, however, it is an important, you know, medium level risk for the treatment, it is typically self limiting and doesn't continue on and on post MDMA. There's also the potential of a very significant risk that's just inherent in studying PTSD, which is suicidal ideation and behavior. And this has to be managed very carefully in the context of our clinical trials, and will likely to continue to be a safety consideration, post approval as well for this population. However, we didn't really have a strong evidence to suggest that it's specifically associated with MDMA itself. We also developed the risk mitigation procedures to ensure that the potential for abuse is mitigated. So the treatment is delivered under a direct observation of clinicians. And as a result, FDA also agreed that this sufficiently mitigates the abuse risk. We also found that there was no evidence of neurocognitive impairment in a couple of our phase two studies, both individually and in combined analyses. And this was also an important consideration due

to some of the stigma associated with MDMA as a potential neurotoxic drug. We also gathered additional information from our phase two studies that enabled us to conduct a preliminary cost effectiveness analysis. So a very important factor in delivering MDMA therapy to patients is that we need to come up with ways of ensuring patient access. And this publication that we put together actually found that this therapy could save costs to the healthcare system within three years post coverage, and a simulation analysis compared to standard of care over a 30 year time horizon in 1000 subjects or patients found that we could potentially save $103 million to the health care system, and over almost 43 deaths in that kind of a simulation analysis. So Amy is going to tell you about the phase three trial.

A Amy Emerson 37:46

Okay, so with all of that phase two data, we look to see what the best design would be for phase three, and we decided on a three session model with a primary endpoint two months after the last treatment. In this way, we really were giving everybody the best chance to have a response, whether they were in the dissociative subtype or not, and kind of no matter the length of their PTSD. So though we had seen the greatest responses. After the second session, we felt like a three session model made the most sense for phase three. It consisted of three, eight hour MDMA sessions about a month apart, and 1290 minute non drug therapy sessions three before the first MDMA session for preparation and three following each. And prior to enrolling in the study, of course, there was a whole screening period to make sure people were qualified for the study. So once they had their screening, and they and they had gone through that process, and the three prep sessions, we did a confirmation of PTSD with the caps five, and we randomized them to either receive MDMA plus therapy, or placebo plus therapy, or you could think of it as therapy alone. So really, it's not placebo, a fully like, placebo controlled study in the way that we're comparing to nothing. We are comparing to therapy alone with a placebo pill. So once once they were randomized to these groups, they stayed in it the whole time. And there was not unblinding after one subject at a time it was in this for the whole study. And there's no crossover within the phase three design. There's a follow up study that takes place after the phase three is over and unblinded for the people in the placebo group to be able to get the full dose treatment. Okay, so this treatment takes place over about 15 weeks primary assessment is two months after the third session, there's about 100 people that we had planned for the study, and this would take place over 15 sites in the US, Israel and Canada. We started our first session with an 80 milligram dose plus an optional half dose, and the second and third treatment sessions had 100 you could go up to 120. You can either stay at 80 or above 220 milligrams, plus the optional half dose. This is this was randomized and blinded. And as you can imagine, blinding is a little bit difficult in a placebo controlled study comparing to MDMA. So this was a big point of discussion with

the FDA. And our way of minimizing bias and the results, which is the goal of blinding was to use a fully independent rater group to do all of the capsule assessments by telemedicine. So these independent raters were well trained, they worked on many PTSD studies, and they've been part of a lot of training and internal validation to do the cops. And they were never in the room with a patient during a session, they only saw the participants during the rating sessions via zoom. And they rarely ever saw the same patient twice with the same participant twice. It was possible but never, they never saw them for two times in a row. So they really didn't have any idea of where they were at, in the study protocol at the time when they were doing the ratings. When I in my past life, when I worked on vaccine studies, this was called an observer blinded design. And this was accepted by the FDA. And we feel like it was a very good way to do to have consistency and bias minimization and our primary endpoint collection.

D Dr. Bera Azhar Klosinski 41:25

So let's talk a little bit about the people who were in the study. Amy, can you tell us about that.

A Amy Emerson 41:31

So first, I'm going to point out the big thing on this slide that probably people are noticing or have heard about before, which is, we did not achieve a representative sample across racial demographics. And this is something that we are still focusing on, we did focus on it during the phase three, we're continuing to focus on it. And we're really looking at it for improvements in our expanded access program as well. But during the phase three study, we did a few things to try to shift this, we reviewed our demographic data on a weekly basis, we met with study sites and therapists monthly to access and implement strategies to recruit people that from underserved populations and people of color. We organized an external Advisory Council that focused on diversity, equity, and inclusion, and they reviewed our protocol, they reviewed assessment tools, training, recruitment of staff, therapists, that all kinds of things to help help us improve in our ability to reach new people. We also provide at our sites with additional budget to compensate participants for study related costs. It's just tough childcare and transportation. The phase three therapists were required to attend a racial justice and micro aggressions training and respond to reflective knowledge assessment afterwards. And still we didn't achieve the goal that we were hoping for, we saw some improvements during it. And we started to think about what could we do to improve going forward, not just in this study, and so one of the other things that we did was plan and implement a therapist of color training to increase the diversity of the providers. This is a much bigger conversation. But there are many systemic reasons that communities of color don't necessarily feel comfortable

engaging in clinical research. There's been a very traumatic history for many communities, both with research and with schedule one drugs. And it's hard to overcome that in a single study. So it's really important that not only us but all of us, all of the community and potential providers continuously work on creating access, so that by the time we reach a post approval world, we're not just beginning to think about equity, but we're already achieving it. We currently have a very active and diverse working group that are looking into ways to improve outreach into communities of color. And this group is working really closely with our research team. Okay, so let's talk about what we did do, which is to we did have a really good representation of women in the study. I think many times when we talk about the PTSD studies, people think that we're treating male veterans. But as you can see, 66% of the study that people in the study were actually women, and only 12% were in the study with a combat related reason for their PTSD. We also had a mean age of 41. And there was no differences. This is very important, no differences in our demographics between our placebo and our MDMA group. And that's, again, important because if there's differences in the end of your study, you don't want it to be because people are questioning that there was a difference in your groups at the beginning of the study. There was also 84% of the people in the study had developmental trauma, and 21%. Were in the disassociative subtype. Now, let's talk a little bit more closely. The trauma history. This just again is this is a breakdown by gender and cause of PTSD and so here you can see Even more clearly what I was saying that the majority of the people entering the study had PTSD related to sexual assault and sexual trauma. And the majority of the people in these groups, except for in the combat exposure one were women. So that gives you a little bit more understanding of that we were really trying to treat the population and what does it look like out there in the real world for PTSD, and this is representative of that. Another important thing to consider is that the the general population for people with PTSD have a lot of comorbid diagnosis, many people entering the study had a history of suicidality, and we did not exclude people with previous attempts of suicide as long as they weren't in the last six months. So there was also important as to show that there was no differences between the MDMA and placebo group in the history of suicidal ideation or positive behavior. And many PTSD studies do exclude people that have attempted suicide before they also exclude people with other common morbidities, such as alcohol use disorder and cannabis use disorder. And we did a lot of work to negotiate with FDA, that there that people were not actively having a use disorder, but that many, many people had had that in their medical history. And this was important to us, because we're trying to be representative of the PTSD population, so that we're actually testing a lot of group of people that would be seeking treatment post approval. So now we're going to get to the results fair, go for it.

D Dr. Bera Azhar Klosinski 46:45

All right. So what we found was quite exciting. When Amy and I first saw these results, I, it was just such a dramatic moment, Amy, how did you feel about it?

A **Amy Emerson** 46:59

I'm over the moon, I couldn't believe it speechless, which is rare.

D **Dr. Bera Azhar Klosinski** 47:05

My thought was that we're gonna try to help as many people as we can, and I think each of us are emotionally connected to this work, as well as just being researchers and scientifically interested in it, because we were trying to help as many people as we can who have PTSD. So what these results are showing is that there was a robust, statistically significant and statistically very persuasive difference between the group who received MDMA from those who received placebo, both in the context of therapy, so the p value is very low, and this means that the chance of a false conclusion is extremely low. We also found that the effect size was large. So the effect size was even larger than our pooled analysis, which was 0.8 for as a reminder. And in addition to this significant improvement in PTSD, we also had a positive secondary endpoint. And the secondary endpoint was the functional impairment that's also highly prevalent, with PTSD. And this one was also significantly improved. And as with any study, it's important to evaluate the quality of the data. So it's important to know how much missing data there was. And our study was impacted at the tail end by COVID. In terms of just introducing difficulties and participating and the treatments themselves for the patients or the participants, as well, as just generally, it was just hard to come to the visits because everybody was concerned about getting COVID. And what we found was also encouraging in terms of the number of dropouts, the there were more dropouts in the placebo group than the MDMA group. And as you can see, the COVID related dropouts were equivalent, but there were just more adverse events in the placebo group than the MDMA group. And we had one participant who chose to discontinue from the MDMA group because they felt an early indications of efficacy of the treatment and didn't feel that they have to continue in order to get benefit. So let's talk a little bit about how MDMA compares to those available PTSD medications that we have compared it to previously. So Paxil and Zoloft have small to medium effect sizes and MDMA has a large effect size and the way we calculate the effect size is by subtracting out the placebo with therapy effect. So in clinical practice, MDMA is designed to be delivered as an adjunct to therapy. So it's likely that the results will be you know, much Better than just looking at the effect of MDMA alone, which is the 0.91. We also had a really interesting finding about the dissociative subtype of PTSD. So we had expected some variability in the treatment outcomes because other available PTSD medications actually don't work as well, for the dissociative subtype of PTSD, either looking at

psychotherapy or medications. And this was the only significant covariant that came out of our analysis was that people in the dissociative subtype, although the numbers are small, appear to do better than the other folks who have the non dissociative subtype of PTSD overall, everybody. Not everybody responds, we did have some non responders, and we're going to tell you about that next. But this is a scientifically really important finding, because it also helps us to understand a bit better about how MDMA may be working, both from kind of combined neurobiology and psychological mechanism of action.

A Amy Emerson 51:06

Okay, so again, we want to look not just at our P values and our effects as we want to look at the how the symptoms of the PTSD are changing. So very similar to what we did in phase two, though this is all in a single study, not a pooled study, we look to see a loss of diagnosis and clinically significant response. So in the control group, 32% of the people with therapy alone, no longer met the criteria for PTSD. So similar to what we saw in the pool, phase two, where it was 23%. And this is, again, on par with standard of care, so this is, you know, it allows us to make a comparison to what is out there. More importantly, we saw in the MDMA group, 67% of people no longer met the criteria for PTSD two months after their last treatment, this is as compared to 56% in phase two, so a slight improvement even over a phase two data. But again, that was a pooled set of data with a couple different study designs in it, and two or three sessions. And this is a three session model. So this is really fast, this is really fantastic for us. And this kind of ties together. So this is what it looks like when you have a really strong p value like we had and a strong effect size, and then loss of diagnosis. The other bit, in addition to loss of diagnosis, we also looked at the clinically significant response. So like the drop in PTSD symptoms, and that was 88% of people had a clinically significant reduction in their symptoms. And this is the same as what we saw on phase two, we also had five non responders and 14 people fully in remission at the end of the study. And as a reminder, when we did the long term follow up, for the phase two data, we saw an increase in people having loss of diagnosis, it went up to 68%. So we're going to do the long term follow up and phase three as well. And we hope to see that even maybe more potentially more people improve as they get further out from the treatment. But at least that there is a durability and response and that the gains that they made are kept. And we'll also be looking to see if there are relapses and trying to understand more about that. So another piece that you want to look at when you're looking at a study is you want to look at your results. And you want to look at the site site differences you want to look at this was another important reason that your demographics are the same between your groups, you want to keep as many things consistent as possible, so that you really know where the differences are. And one thing about going from single center studies into multi site, large multi site study with really basically almost all new therapists that this was their first time working on MDMA assisted

psychotherapy, we weren't really sure if we were gonna see site to site differences. We were hoping no and that, and that was the case, our results were evenly distributed. It wasn't that the most experienced therapists were getting the best results. And so this speaks to a couple of things. One, MDMA works well, and maybe the MDMA and the way that we approach the modality where it's geared towards the participants experience helps to create a quality around the way that all people respond. And it also means that hopefully, our therapy training program is working really well. And we have an amazing denigrate dedicated group of therapists, as well working on these studies. And we're really grateful for the time and energy that they put into working on this study.

D Dr. Bera Azhar Klosinski 54:43

As well as the therapy training team and the clinical supervisors who help support them and getting those results. Yeah.

A Amy Emerson 54:53

So you can also have a really great study that's really efficacious, but if you have a lot of adverse events, like Then there's another whole piece to deal with. And you know, you want to have something that's efficacious and safe. So I'm going to tell you a little bit about that now. We collected series, we collect adverse events that are happening in the study, and you collect serious adverse events, meaning something that's life threatening, and we are collected adverse events of special interest. So these were things that we agreed with FDA would be things specifically to look for in our MDMA study. So three categories suicidality, cardiovascular and abuse potential, and then the, the other benefit of having a placebo controlled study is that you can really be in to see what is a background rate, which and what is truly related to MDMA. And so we didn't have as many placebo controlled studies in phase two. So it wasn't as clear that we could say some of the things were background rate, but now we have stable control data. And we have another study underway, that will give us even more of that. So as you can see, we had really minimal events in the MDMA group across all of these categories. So most notably, there were 10 events of suicidality across five people, all occurring in the placebo group. And this is to be expected in a PTSD population. And there were only three events in three people in the MDMA group. And again, these were adverse events or special interest, these were not serious adverse events. In the serious adverse events category, we saw none in the MDMA group, and two in the placebo group. One person attempted suicide twice, and another was self hospitalized with severe suicidal ideation, but no attempts. So this was very good news. For us, it really does feel like we can say that the suicidality is a background event and actually that the MDMA could be improving the suicidality for people with PTSD. So let's look at also just treatment related adverse events

that are non serious. So these are just the most common things that are reported by the participants in the study. It's not very exciting, which is a good thing. And they were self limited, they usually resolved within a few days post dosing, and the most frequent non serious adverse events for the MDMA group, so related to MDMA were muscle tightness and decreased appetite. This was very, very good news for us. We took that information from phase three plus the information that we had from phase two. And we put together a program level risk summary. So there's a really specific way that FDA refers to your risks, they call it a high, medium and low risk. So high, a high risk in a study means that you have to add a bunch of new complex procedures to eliminate or manage that risk. Medium means that you might have to do some procedures, they're not too complex, but they help you to manage the risk and low is that no additional procedures, they're not complex, you're not, you know, you're just doing normal things for screening. So when you put all of ours together, our program has no high level risks. We have medium level risks in the cardiovascular area, and the procedures that we put in place for really around screening to rule out underlying cardiovascular disease. And the other area was along the psychological distress, and the things that we put into place where therapy integrated visits and phone calls to check on people after their treatment, and an escalation plan in case of suicidal ideation or behaviors during the treatment. And then our low level risks were thermo regulatory, and we really didn't have to do anything complex, like we have blankets, and you have temperature control for the MB the ambient temperature. So you know, nothing complex at all. And then the other was osmoregulatory. What. So with this, we managed it by water intake is limited to no more than than three liters, and we encourage electrolyte containing fluids to be consumed. The other low level risk is reproductive developmental, and we have pregnancy tests before they're saying and contraception requirements for the study. So these are all very easily managed, as you can say, which is, again, good news for the program. It's very efficacious, efficacious and safe, and it's not like these areas are not complex. We also saw one expected serious adverse reaction though in this was an exacerbation of a pre existing ventricular extra Sicily's, so this is a kind of arrhythmia that's happened in one person out of 341. So it's less than 1%. And we saw, as far as the suicide risk, we actually saw that MDMA reduce the risk of suicide when you compare the rates in the placebo group versus the MDMA group. And so we feel at this point that we can say based on In our data and the literature that serious adverse events are rare in MDMA clinical trials. So in summary, if you take a look at our whole program, we have very small p values for our studies. So this is robust, and we have a large effect size. And we have been able to replicate results across studies, we have no site to site variability, and we have a very good safety profile and no increase in suicidality. So we have a very positive risk benefit ratio. And this is exactly the kind of package that you're hoping for, to go to the FDA with for a new drug application.

D

Dr. Bera Azhar Klosinski 1:00:39

So with these results in hand, we've been currently engaged in increasing the current commercial manufacturer of MDMA. So in December of 2020, we completed the commercial manufacturer for the MDMA drugs substance, and now we're working on formulating this MDMA into the capsules. And we're also working on stability experiments that are important for setting the shelf life. So once MDMA is shipped out to clinicians, how long is it good for and that work is is actively ongoing right now, we're also engaged in developing our global regulatory strategies. So we just enrolled our first participants, our patients in Europe, in Norway, today, and March 26 2021. And we're also actively screening participants in the Czech Republic and the Netherlands, currently. And so hopefully, we'll be able to interact with as many regulatory agencies as we can to get their input on our program, and whether our, our data package will be sufficient for them to approve MDMA and those countries and we really feel strongly that it's important for all patients to have access to this treatment if they want it. Another really exciting program is that we received permission from FDA as well as Israel to launch a compassionate use program with access to 50 patients in each country, for who, for those who are suffering from treatment resistant PTSD. And this is also an opportunity for us to try to give hands on practice to more diverse therapists of color, and support our goal of inclusion and promoting patient access for all patients. And we're in the process of establishing centers of excellence, and preparing a therapist workforce and a network of clinics that will be available to deliver this treatment, once regulatory approvals are received. And we are also in the process of gathering safety related health outcome data, to support insurance, interactions and build a business case for payers. And we feel we know that this treatment is not necessarily accessible to many people. And we feel that developing your reimbursement strategy is really important, very close to launch. So Amy, how can people participate in the clinical trials?

A

Amy Emerson 1:03:36

So you can go to clinical trials.gov and search for MDMA PTSD, in fact, any clinical trial that's going on in the US, you can find it listed here. And you can revisit our recruitment website, mdmaptsd.org, and you can participate in other ways with the therapist training program. And talking about this program is another great way to help us and to participate, consider telling doctors, colleagues, other people, family members about the work that's being done, because we have a lot of reeducation that needs to happen in order to make this available to everybody. So it's been great sharing this information with you all today. Thank you.

D Dr. Bera Azhar Klosinski 1:04:19

Thank you very much for your attention and we look forward to hearing from you guys in the future.

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