Advancing Psychedelic Clinical Study Design
Virtual Public Meeting
Day 1: January 31, 2024 | 10am-2pm *(eastern)*

Transcript

Welcome
Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler (00:00:31):

Hello and welcome to day 1 of our two-day virtual public meeting. I am Susan Winckler and I have the honor of serving as the Chief Executive Officer for the Reagan-Udall Foundation for the FDA. We are pleased to be working with the US Food and Drug Administration to host this virtual event. And thank you for joining us today, and we hope that we will see you tomorrow as well.

(00:00:52):

Over the course of those next two days, we will be exploring the scientific issues that arise while working with psychedelics in clinical trials and drug development. This meeting builds on concepts that were highlighted in the psychedelics guidance issued by FDA in June of 2023. Before we begin, I need to run through just a few housekeeping issues. Because of the size of the meeting, attendee cameras and microphones are off throughout the event. We have a fantastic lineup of speakers and reactor panelists. And thank you for submitting questions during the registration process. We have used those to inform the discussion that we plan to have today. We may have a few moments in each session to address the audience questions, so submit those through the Q&A function. And then finally, we are recording the meeting and we will post the recording along with the slide deck and the transcript on the Foundation website next week.

(00:01:53):

So let's talk a little bit about the agenda that we have today. So in just a moment, I'm going to be turning the microphone over to Dr. Patrizia Cavazzoni from FDA to offer opening remarks. And then we will move through a series of sessions where we will hear first an overview of the June 23 draft FDA guidance for industry on clinical trials with psychedelics, then explore the experience of scientists in FDA-authorized clinical studies and consider aspects of psychedelic clinical trial design. The full agenda as well as other meeting materials are available on the Foundation website at reaganudall.org, and the link is posted in the chat. With that, I am going to get out of the way and open up with our opening remarks. And so to kick off our event, I welcome Dr. Patrizia Cavazzoni, who serves as the Director of FDA Center for Drug Evaluation and Research.

(00:02:51):

Dr. Cavazzoni, thank you so much for joining us. I'm going to go off camera and we look forward to your remarks.

Opening Remarks

Patrizia Cavazzoni, MD, Director of the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration

Dr. Patrizia Cavazzoni (00:02:59):

Good morning. Thank you, Susan, for that kind introduction. Good morning everyone. On behalf of FDA, welcome to this important workshop. It is an honor to speak with you today. First of all, I'd like to thank the Reagan-Udall Foundation and the FDA Planning Committee for their efforts to convene this meeting. And to our speakers, panelists and attendees, thank you for taking the time to participate in what should be a fascinating set of discussions.

(00:03:27):

I should note here, and you will hear this multiple times throughout the workshop, that FDA has not approved any drugs containing MDMA or psilocybin as being safe and effective for any therapeutic use. However, we certainly recognize that there are been growing interest in the therapeutic potential of psychedelic drugs in recent years. Psychedelics are being evaluated for use in the potential treatment of a number of conditions including depression, post-traumatic stress disorder, and substance use disorder. We also recognize that in the real world, many people are currently using psychedelics outside of clinical trials. In fact, according to the National Survey on Drug Use and Health, an estimated 3% of people age 12 and older or 8.5 million people used hallucinogens in the past year. Given these realities, this workshop is an important opportunity to expand their knowledge about psychedelic clinical trial design, as well as to explore considerations for current use of psychedelics and potential future use of psychedelic drugs.

(00:04:41):

In the event that a psychedelic drug is approved as safe and effective, this type of exploratory conversation on potential future use will help repair our key partners and the patients they serve for what comes next. This workshop is part of FDA's comprehensive approach to exploring current use and potential future use of psychedelics. So I'd like to briefly tell you about some of our other recent activities. These activities broadly fall into three categories, our 2023 draft guidance, our participation in meetings on psychedelic drug development, and our support of research on psychedelics.

(00:05:24):

First, in June 2023, we published the first FDA draft guidance that presents considerations to industry for designing clinical trials for psychedelic drugs. My colleague, Dr. Tiffany Farchione, will provide an overview of this draft guidance in the next session so I will leave further details on the guidance in her capable hands. But I do want to note that we appreciate the robust feedback that many of you provided on the guidance through our federal register notice, and we're currently reviewing these comments.

(00:05:59):

In the past few years, we have also participated in meetings and conferences on psychedelic drug developments that helped pave the way for today's workshop. For example, in 2021, we co-hosted a meeting with the Duke-Margolis Center for Health Policy to discuss developing and regulating psychedelic for therapeutic use. Finally, we're funding a few research projects on psychedelics, including one program that looks at the real world experience of people using psychedelics.

(00:06:29):

Another project aims to understand the behavioral, social, and economic factors that may influence purchase and use of psychedelics. Such projects helping form our broader understanding of

psychedelics, again, recognizing the importance of exploring current use and potential future use of psychedelics.

(00:06:51):

Over the next few days, we look forward to hearing from stakeholder stakeholders committed to advancing scientific understanding in this emerging space. We also know these complex discussions about clinical trial designs and considerations for current use and potential future use are wrapped up in equally complex issues of health equity. Throughout our speaker's presentations, our panelists reactions, and our audience members' participations, we hope to learn from the researchers and clinicians, patients and individuals with lived experiences, industry members, and federal, state and tribal partners. And we hope this conversation will help inform the broader context and understanding around FDA's regulatory decision-making. With that, I'd like to thank you all for coming and being part of this thoughtful discussion, and I'll turn it back to Susan.

Session 1: Overview of FDA's Psychedelics Clinical Investigation Guidance

Tiffany Farchione, MD, Director, Division of Psychiatry, Office of Neuroscience, Office of Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (00:07:53):

Wonderful. Thanks so much, Dr. Cavazzoni, for setting the stage for our discussion today and tomorrow.

(00:08:01):

So let's jump right in. Our first session is an overview of FDA's Psychedelics Clinical Investigation Guidance. There's a link to the guidance in the chat if you have not yet reviewed that document. So to hear about the guidance, I'm going to turn to Dr. Tiffany Farchione, who is the Director of the Division of Psychiatry within the Center for Drug Evaluation and Research at FDA. Dr. Farchione, the floor is yours.

Dr. Tiffany Farchione (00:08:30):

Okay. Thank you so much, Susan. Let me just make sure I can move these forward. There we go. All right.

(00:08:38):

So as Susan mentioned, my name is Tiffany Farchione. I'm the Director of the Division of Psychiatry in the Office of Neuroscience at FDA. And today I'm going to be giving just a broad overview of the draft guidance that we published last year on Psychedelic Drugs: Considerations for Clinical Investigations.

(00:08:58):

And before we get started, I do want to note that although the title of my talk refers to psychedelic drugs, and I'll be using the term 'psychedelic' throughout my presentation, I'm really using that as a catch-all term that includes both classic psychedelics, like psilocybin, and also entactogens like MDMA. So it's really more shorthand than technical terminology. And also I want to point out that as a government employee, I have no conflicts or financial interest to disclose.

(00:09:29):

Okay, so you've likely noticed that there has been a lot of buzz about psychedelics these days. This is just a small sampling of recent headlines and including two hot topics, psychedelics and AI, and one fell swoop. But obviously, there's a lot of excitement about the potential for psychedelics to transform the treatment of psychiatric and substance use disorders, or even just to improve overall wellbeing. The

general tenor of all of these articles tends to be one of inevitability. But as anybody who's ever heard me talk about psychedelics before, knows this is putting the cart before the horse.

(00:10:09):

From a treatment perspective, and as Dr. Cavazzoni already mentioned, these are still investigational drugs. We have not approved any psychedelic for use in clinical practice. So the clinical trials that are out there, they look promising. And as someone who, honestly, I am almost pathologically optimistic, I get excited about this stuff too, but I've also been around long enough to see some very promising programs ultimately fail in pivotal trials. So I think it's important to take a step back and talk first about the work that still needs to be done.

(00:10:46):

So today I'm going to talk a little bit about... Oh, wait a second. There we go. Oh, this is going really fast. Sorry about that. Today I'm going to talk a bit about the evolving landscape of psychedelic research and why we felt it was important to publish a guidance now. I'll provide some high level regulatory background and then walk you through the topics that are in the draft guidance as well as some of our thinking behind the recommendations that we put in that document. And then finally, I'll spend a bit of time discussing some of the unique challenges that are associated with the clinical trial design for these programs and set us up for the rest of the workshop. And some of those challenges are listed here on the slide. Here we go. No doubt you've noticed that there's been a huge resurgence in research on psychedelics in recent years, and we're certainly seeing that as well. There we go. The two figures that are on this slide, those include both commercial and research investigational new drug applications, or INDs, that we've gotten in the Division of Psychiatry. That's the DP that's noted on the slide there. So that's development by pharmaceutical companies as well as studies by academic investigators, but only in our Division in Psychiatry. This doesn't include, for instance, studies that look at psychedelics as potential treatments for substance use disorders. Those are all in a different review division. But what you see here is that on the left we have the number of new INDs that we've received. And then the right shows the percentage of our overall new IND submissions. So these are just the new applications. It doesn't include the number of new protocol submissions or meeting requests that we get for open IND.

(00:12:44):

Essentially, the bottom line here is that psychedelic applications have become a sizable chunk of our overall workload. But the good thing about reviewing so many protocols and development plans in a short timeframe is that we very quickly started to identify some recurring themes. And we've noticed that we were giving similar advice in response to similar issues across multiple programs and sponsors. So we started to keep track of that advice in an effort to maintain some regulatory consistency. And then ultimately, it just became clear to us that the most efficient way to disseminate our advice to all sponsors and investigators in this space was to publish a draft guidance.

(00:13:24):

So for those of you who are outside of the pharmaceutical industry, you may not be familiar with FDA guidance documents. And essentially, these are documents that describe our current thinking on any given topic. They aren't legally binding, but they do represent our best advice and are intended to be helpful and to provide transparency in our decision-making. So there are all sorts of guidance documents covering all sorts of topics, but you can easily search on our website to see if we have any advice to offer on the particular topic you happen to be interested in.

(00:13:56):

So just to give you an idea, I have a few examples of guidance documents related to clinical trials. So to support a marketing application, a company has to provide substantial evidence of effectiveness for the

drug. And we have a guidance that describes in detail what that means and how it can be demonstrated. Once effectiveness has been demonstrated and we've determined that the drug has a favorable benefit-risk profile, then we need to be able to write a label and ensure that the label contains the essential scientific information needed for safe and effective use of the drug. That label needs to include information about the disease or condition that the drug is intended to treat, the dose and frequency of administration necessary to achieve a therapeutic effect, a description of the risks associated with the drug and how those drug risks can be mitigated, and then as well as information about the adverse reactions that were observed in clinical trials.

(00:14:53):

And of course, we need to be able to describe the clinical trials that supported approval, including a description of the design, the endpoints, and results. So basically, I'm showing you all of these guidances as a reminder that the framework that we use to evaluate every other drug development program applies here as well. And now, we have a guidance that specifically outlines some of the foundational constructs that all sponsors, including academic sponsor investigators, should consider when studying the therapeutic potential of psychedelic drugs.

(00:15:25):

So over the next few slides, I'm just going to walk you through the advice that's in that guidance. So the document is organized in what I think of as a translational order. So we start at the bench with chemistry, manufacturing and controls. And from there we move to animal studies with our non-clinical advice. After that, we get into humans with the sections on Clinical Pharmacology, Abuse Potential Assessment, and then finally move to the bedside, end of the bench to bedside spectrum with advice on clinical study design.

(00:15:55):

So starting with CMC, we need to make sure that the drug is what you say it is and that it is consistently what you say it is. So sponsors have to provide enough information that we can ensure proper identification, quality, purity, strength. We remind folks in our document that the chemistry data submitted to FDA may be proprietary. So that means that sponsors who are doing clinical work with a psychedelic either have to generate their own data or they have to establish a right of reference to another sponsor's data by getting a letter of authorization from a company that's been allowed to conduct research under an IND already.

(00:16:32):

And then we also referred sponsors to our botanical guidance to help them determine whether their investigational product would be considered a botanical or not. These were all things that most sponsors did include in their submissions, but there were enough of them that we thought it was important to add these points to the guidance. But the CMC issue that more frequently led to delays in development had to do with CGMP, or Current Good Manufacturing Practice. So programs would be delayed. We even put some programs on clinical hold, which means that a study can't legally proceed, all related to the lack of drug substance for FDA assessment or inadequate controls for their phase of development.

(00:17:15):

So as an example, we always recommend good manufacturing practices during any phase of development, but our regulations say that phase I drugs drug substance is exempt from being manufactured in a CGMP-compliant facility. I know it sounds like technical jargon, but the phase I are the early studies. And as you go through phase 2, 3, 4, it gets later and later in the development for those, again, who aren't familiar with the terminology.

(00:17:43):

So as the drug production is scaled up and the batch size increases, quality controls become more stringent. And anybody who is conducting a study that's either exploratory or proof-of-concept in patients with a psychiatric condition, we consider that a phase II study. So that means it has to be manufactured in a facility that meets CGMP standards.

(00:18:07):

Okay. All right. So nonclinical studies help us to inform our understanding of the drug's pharmacology and toxicology. And these can include acute, subacute, chronic toxicology, developmental and reproductive toxicology, carcinogenicity studies, and more. So our regulations are inherently flexible and the exact types of studies that are needed to provide this data aren't specified. But the types of studies considered appropriate to address these issues are largely described in FDA and international counsel on harmonization guidances. So we've allowed clinical studies with certain psychedelics and entactogens to proceed even in the absence of typical animal toxicology testing, but only if there's been extensive human exposure to that specific drug in previously conducted clinical studies and there weren't any serious safety concerns from the trials.

(00:19:05):

So we also include a note in the guidance about evaluating serotonin, or 5-HT, receptor binding. This is important because we know that psychedelic drugs have 5-HT activity, and we know that 5-HT2B receptor binding has been linked to heart valvulopathy in humans. So this has implications for the design of certain nonclinical studies.

(00:19:27):

Then finally, even though current psychedelic drug development programs are exploring mostly single dose or intermittent dose treatment paradigm, most of the conditions that are being studied, at least in psychiatry, are for chronic disorders like major depressive disorder, PTSD. So I want folks to bear this in mind when we talk about durability of treatment response later today. This is a major unanswered question. So until we know how long a treatment effect lasts and whether and how often re-dosing might be necessary, we don't know yet whether chronic toxicology studies are going to be required for these programs.

(00:20:10):

All right, so clinical pharmacology. These are the studies that help us to characterize the pharmacokinetics and pharmacodynamics of different drugs. And in this section of the guidance, we remind sponsors of the need to evaluate food effective drugs, drug-drug interactions, drug-disease interactions, like studies in organ impairment and so on. We note, again, the potential for cardiac valve stiffening with long-term exposure to 5-HT2B agonists. And for now, we just recommend excluding subjects who have preexisting valvulopathy or pulmonary hypertension from multiple-dose studies until we can better characterize that risk. So this is another area, again, where we'll be able to give better advice when we have a better idea of the ultimate dosing paradigm for any given drug.

(00:20:56):

All right. So we also highlight a few potential pharmacodynamic drug interactions for sponsors to consider when designing their trials. In the document, we note that chronic use of SSRIs or MAOIs might reduce the effects of a psychedelic drug and that chronic use of tricyclic antidepressants or lithium, or acute use of SSRIs and MAOIs, might potentiate the psychedelic effects. And we list these not to say that you should exclude people who are on these medications from your trials, but rather it's to make you

aware of the potential interactions so that you can consider this when designing your studies, consider the potential impacts on the data and plan accordingly.

(00:21:37):

And finally, we make the very important point that the dose-response relationship from most psychedelics is really poorly understood, and that it's important to characterize this relationship in your clinical studies both for safety and for efficacy. So there's a fair amount of information in the guidance about the abuse potential assessment, and I'm not going to go into a lot of that here. But bear in mind that an abuse potential assessment must be submitted with a new drug application for any central nervous system active new molecular entity and for drugs that are already controlled under the Controlled Substances Act. And psychedelics meet both of those criteria. They're currently classified as Schedule I under the CSA because they have a high abuse potential and don't have a currently accepted medical use. But if one were to be approved, the abuse potential assessment would assist in determining an appropriate rescheduling action.

(00:22:38):

So it may be possible to use published literature to support some aspects of the abuse potential assessment if the drugs have been well characterized in previous studies. And our guidance on the assessment of abuse potential drugs describes everything that's needed for an abuse potential assessment. But one thing that's important to remember is that if you are conducting research with a Schedule I drug, you do need a DEA registration in order to legally do that work.

(00:23:10):

All right. So now we're going to get into the actual clinical trials themselves. And as a reminder, the standard for substantial evidence for psychedelics is the same as it is for any other drug. But what does that mean? So typically... Oops, hang on. So typically that means too adequate and well-controlled clinical studies, and we'll get into what makes a trial adequate and well-controlled in a moment. And how we're designing adequate and well-controlled studies of psychedelics can be complicated. So let's talk a little bit about the kinds of things that complicate these studies and make their results more difficult to interpret.

(00:23:54):

So for starters, in most of these studies, you have an highly engaged therapist or monitors who are in the room with the subject the entire time that they're experiencing the psychedelic effects. You have significant patient and therapist expectations that are probably fueled by the highly favorable media coverage. You have an elaborate therapeutic intervention, which is the kind of thing that would normally increase placebo response rates. And then there's also dramatic functional unblinding. So people who've gotten a psychedelic generally know that they've gotten the active drug because of the intense perceptual disturbances that they experience.

(00:24:37):

And then finally, psychedelics also appear to have some unique suggestibility properties. So in that context, what's the therapeutic impact of telling patients, "This is really going to help you" when they're in that suggestible stage? So each of these elements can impact the therapeutic response. So it's important to tease out the contributions from these various issues in order to avoid ultimately approving a placebo that's just wrapped in a complex therapeutic milieu.

(00:25:12):

So our draft guidance addresses some of these concerns and provides some suggestions for managing the issues in clinical trials. But it's important I think for us to note that we don't have all the answers. We

don't have a specific recommendation for how to do these studies the 'right' way. That's why we describe trial design elements for sponsors to consider rather than characterizing them as best practices or standards in the guidance.

(00:25:40):

All right. So let's talk a little bit about those adequate and well-controlled studies that contribute to substantial evidence. And we'll ultimately be described in the Clinical Study section of a label if a drug is approved. So the features of an adequate and well-controlled study are described in the Code of Federal Regulations. So that means that not only... So they're not our current thinking or helpful advice, they're binding. So I'm going to just highlight a few of those. So first up, we have that the study uses a design that permits a valid comparison with a control. So that's typically a placebo control study. Adequate measures are taken to minimize bias. So this is where blinding usually comes into play in clinical trial design. And then the methods of a subject's response are well-defined and reliable. So that's basically the endpoints that you are using in the study, like having specific rating scales to assess symptoms. It's not enough in a clinical study to just say, "Do you feel better?" And it's a yes or no, and if you have more yeses, that's good enough. That's not good enough.

(00:26:56):

So that's as much as I have to say about methods of assessment for now. We do of course, have a guidance related to clinical outcome assessments as well, but it's not covered specifically in the psychedelic guidance. So I'm not going to talk about that anymore today. But I'm going to talk about these first two bullets in a little more detail because they are covered in the guidance. I will note that they overlap and are interrelated, but I'm going to try to separate them out a bit for the purposes of the talk.

(00:27:28):

So let's start with the design that permits a valid comparison. So even though I've split these two topics, again, like I said, they do kind of bleed together. And various sponsors have taken various approaches to dealing with this each with its own set of pros and cons. So in the context of psychedelic drug development, the use of a traditional placebo as a control can be problematic, in part because the subjects who are getting the active drug experience that functional blinding that I talked about earlier. But also in that context, a subject who gets a placebo when they have high expectancy, they might actually experience what's called a 'nocebo effect,' which basically means that they realize they didn't get the active drug and so then they end up feeling worse.

(00:28:24):

So some psychedelic researchers have used other psychoactive drugs as active comparators, things like methylphenidate, benzodiazepines, or even just niacin because of the flushing effect. But this introduces a difficulty because you have to pick a drug that has similar subjective effects. And let's be frank, nothing really has the similar subjective effects of a profound perceptual disturbance that you see in psychedelics, but also that the drug is not known to be therapeutic for the condition you're trying to assess. So it gets complicated.

(00:29:03):

Another potential alternative is the use of sub-perceptual doses of psychedelic drugs. And so they may still have some psychoactive actions and that could reduce the statistical power and increase your likelihood of a type 2 error, which again, I realize is very technical. But it's also possible that you could have a dose that has a therapeutic effect even though you think it doesn't. So it's not really a control. But in some cases, a lower dose of a psychedelic can actually have a negative or aversive effect. So those are all things to consider when you're trying to choose your comparator in a study of psychedelics.

(00:29:48):

All right. So we've said this a number of times. It is extraordinarily difficult to blind these trials. So in the guidance, we offer some suggestions in order to help minimize potential biases. So we talk about using a blinding questionnaire, so that can be helpful not necessarily to reduce the biases, but at least to assess the impact of any unblinding.

(00:30:18):

Another strategy is to use video or central raters who are blinded to treatment allocation and then also preferably to visit number. Video ratings can also allow for some quality control because you can make comparisons between raters and calculate inter-rater reliability scores. And then in traditional trials, with the exception of the pharmacist, everybody is blinded to treatment allocation. And here in a lot of the psychedelic sessions, the therapist who's monitoring the session can also usually figure out the treatment assignment by observing the patient's behavior. So sponsors could consider having one person serve as the in-session monitor and a different person involved in the post session psychotherapy.

(00:31:07):

So we did get a lot of comments about this suggestion. This wasn't, "Our preference is, this is our suggestion is" because we recognize that there's a potential trade-off here. So having the same person serve in these two roles could impact efficacy because of their knowledge of treatment could bias the delivery of therapy and tip the scales in favor of the drug. But then also using two different people might disrupt the therapeutic alliance and then downstream possibly diminish the overall treatment effect. So that said, the contribution of psychotherapy to the overall treatment effect hasn't been characterized yet. So if you are incorporating any type of therapy in your trials, you really need to describe your plan for minimizing bias in the trials.

(00:31:56):

So I think one other option that is out there is that a dose-response trial is another type of adequate and well-controlled study that you could conduct, that it really offers a potential alternative to some of the traditional models with placebo or with having an active comparator if there is no placebo group. Now, if you have multiple different doses, at least two doses of the drug are compared. This can serve as one of the adequate and well-control trials and could potentially solve some of these problems using different complimentary designs. So one placebo control trial to help us assess safety. A dose-response trial can help with the efficacy assessment, but that could be one strategy to demonstrating substantial evidence. So your substantial evidence doesn't have to be two trials designed exactly the same, I guess is the bottomline, take-home point there.

(00:33:04):

So I think that other than the psychotherapy section, the section of the guidance that got the most public comments was the section on monitoring requirements. So I want to talk a little bit about our thinking behind the current requirements, which you see listed up here. So we're very concerned about subject vulnerability during the psychedelic session. Subjects who are receiving active treatment with a psychedelic drug can remain in a vulnerable state for as little as a few minutes with certain fast-acting drugs to as long as 10 or 12 hours even. So we've required that every psychedelic session has two monitors. And we've framed this as a safety issue because then we can put trials on clinical hold if we feel like it's not safe to proceed with that trial. So we've said that at least one of those monitors has to be somebody with graduate level training, clinical experience psychotherapy, and licensed to practice independently. We want to make sure that somebody has their professional license on the line when they are in the room with that patient.

(00:34:19):

And then you'll also note that the credentials here for both the lead monitor and the assistant monitor involve training and experience in psychotherapy. And we felt that that was important because if a subject is having an aversive experience, that training in psychotherapy and that experience in a mental health setting will leave them well-prepared to deescalate the situation. So that was our thinking behind that. So the rest of the guidance lists a few more clinical issues to consider, some of which will have entire sessions during this workshop. We repeat the importance of characterizing the dose-response relationship. So I've said this before a couple of times today, that the dose-response curve for both safety and efficacy is poorly understood. This is one of the things that makes a dose-response trial attractive. We don't know what dose is actually required for a therapeutic effect. So maybe you can get a therapeutic effect without the prolonged impairment that comes with a psychedelic effect. Also, what if there's a serious safety concern in phase 3? Maybe a lower dose could have a better benefit-risk profile even if the overall benefit is slightly lower. So I think there'll be plenty to consider in the session on dosing later on today.

(00:35:36):

We also note that sponsors should plan to characterize the durability of response for their product. We need to understand how long the effect lasts and what is the appropriate inter-dose interval. So depression, PTSD, most of the conditions for which psychedelics are being evaluated are all chronic disorders that generally require chronic treatment. Our a priori assumption is that the symptoms will come back if you don't continue to treat. So we need to be able to write a label that includes information about more than just the first dose or two. So again, I expect a rich discussion on this topic in the afternoon today.

(00:36:15):

And then we want to understand the risk mitigation strategies that are used in clinical trials so we can think about how they might translate into clinical practice. So I'll probably touch on this a bit tomorrow and I discuss the limits of our regulatory authority. And then we also have our final session in the afternoon tomorrow as well. So finally, we let sponsors know that the public health effects of psychedelic will be part of the overall benefit-risk assessment when they do submit a new drug application. And again, there will be some discussion on the public health impacts in the final session tomorrow. While the guidance outlines our current expectations as I've mentioned a few times now, there's still a lot that we don't know and we hope that the sessions today and tomorrow can actually help to fill some of those knowledge gaps. And I think we have a very exciting program set up for all of you, and I'm really looking forward to the presentations and discussions. So thank you.

Session 2: Psychedelics Study Design, Control Conditions, and Blinding

Suresh Muthukumaraswamy, PhD, Associate Professor, Pharmacy, University of Aukland
Franz Vollenweider, MD, FMH, Chief Psychiatrist and Co-Director of the Center for Psychiatric Research, University of Zürich
Matt Butler, MD, Doctoral Clinical Research Fellow, King's College London
Michael Davis, MD, PhD, Chief Medical Officer, Usona Institute
Bernard Fischer, MD, Deputy Director, Division of Psychiatry, Office of Neuroscience, Office of New Drug, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (00:37:14):

Fabulous. Thanks so much, Dr. Farchione. That kickoff is really helpful, including the dynamics of the regulatory requirements versus the suggestions in the guidance. And I'll note we've had a number of questions that are submitted. Some of those have already been addressed in this opening session and some will be addressed as we continue our journey through today and tomorrow. So thank you for that stage-setting session one.

(00:37:41):

We'll now move to our second session, which is going to explore the psychedelic study design, control conditions and blinding. And we are just going to roll right into this session and we'll focus on challenges in selecting control conditions to create blinding for the studies to reduce bias and to determine whether changes in outcome measures can be attributed to the psychedelic. In this session, we'll have two overview presentations and then discussion facilitated with a reactor panel. Our first presenter is Dr. Suresh Muthukumaraswamy, who is an Associate Professor of Medical and Health Sciences at the School of Pharmacy at the University of Auckland in New Zealand. So thank you for joining us from around the world. Dr. Muthukumaraswamy, I am going to step aside and let you pick up the presentation.

Dr. Suresh Muthukumaraswamy (00:38:40):

Okay, thank you for the invitation to speak today. It's a little early where I'm at the moment, still only 4:40 in the morning. So hopefully I'm coherent enough. I would like to just acknowledge some of the colleagues who have made intellectual contributions to some of the things I'll say today, but also acknowledge that the blame for the things that I'm about to say today rests entirely with me. A few disclosures around some of the funding that I currently and have had, and to note the things that I'm going to speak about today come in four different source papers that I've published over the last three or four years. And these are here, and hopefully the links to these will be in the webinar chat. And also since you've got the slides available to you, you can look those up more detail.

(00:39:34):

The first one of the papers is quite long. The second one is more of a readable thing. The third one is more for the humanities. And the fourth one is a sort of more technical approach. And since I'm at an FDA thing, I'm a foreigner, and I don't often spend much time reading the Code of Federal Regulations, but I thought I'd take a look at that and it's informative for what I'm about to talk about. So to establish a drug's effect, it is essential to distinguish the effect of the drug from other influences such as spontaneous change or the placebo effect. And this is the basis for an adequate and well-controlled investigation.

(00:40:15):

And then they go on to say, poor execution can render a trial of any design to be not adequate or well-controlled. An example being a randomized, double-blind, placebo-controlled trial in which unblinding is common due to the effect of the test strike. And that's going to be the topic really of my talk today. And just a single exemplar study not to pick on any particular group as all our groups are affected by this, but you can see here a typical result you might get in psychedelic clinical trial. And when you look in the discussion, you can see the reporting of the unblinding. You can see that 95% of the people in the active group were able to identify the condition they were in. And about 85% of those in the placebo group worked out which group they were in. So the study is, is it really double-blind, is the question we could ask. So Stigetti and colleagues argued that really we should call this a placebo group rather placebo control because the control has actually failed.

(00:41:24):

And so the problems of blinding and expectancy can be summarized in this quote, "Given the obvious psychoactive effects of psychedelic drugs, those in the active intervention group will know they've received the treatment and therefore may show a greater treatment response due to expectancy effects. But those who are in the placebo intervention will know they've received the placebo and disappointment may decrease the placebo response." And I'd just like to clarify that the disappointment response isn't actually a nocebo response, and nocebo response is when you have an expectation of a negative effect from a treatment and that causes the treatment to have a more negative effect than otherwise.

(00:42:05):

We often get caught up in the abstract of these things. So I'm going to play you a video. It's turned out a little bit on the screen.

Speaker 1 (00:42:11):

They didn't hesitate-

Dr. Suresh Muthukumaraswamy (00:42:13):

But it shows you actually what participants might experience in a clinical trial. And it also helps to elucidate with some [inaudible 00:42:19].

Speaker 1 (00:42:20):

... evolve. I just started to go on this amazing journey.

Dr. Suresh Muthukumaraswamy (00:42:25):

One of the patients in this trial. You can see the treatment room. One of the things to note, speaking is to note the closeness of the therapist. They seem to be engaged.

Speaker 1 (00:42:42):

I haven't really cried properly for a long time. But I didn't feel scared or frightened. It felt okay. I was lying there and I just, the tears were pouring out of my eyes. But they weren't sad tears. They were joyful tears.

Dr. Suresh Muthukumaraswamy (00:43:00):

Let's skip over that. You can look that up online. But one of the ladies, the next participant that would've been shown was in the control group. And actually she clearly articulated that she was able to work out, she was in the control group and she said, "I was angry at the trial because I was in the placebo group."

(00:43:21):

So stepping back from the individual view of patients, we can actually consider what the randomized control is actually doing from a formal perspective using the modern science of causal inference. And this uses the Rubin causal model to identify what actually our treatment effects actually are from a formal perspective. And one of the things that is nice when you can start to notate it like this is that you can be very explicit about what the assumptions are for your treatment effect to be credible. And causal inference, essentially we're just looking at the difference between two groups, has four key assumptions. The first one is that you have no interference between the participants. And the second one is that you have no hidden variation of treatments and you need to be able to identify the effect.

And what we're going to see is that these upper two assumptions are often violated in psychedelic clinical trials.

(00:44:27):

A normal RCT meets the causal inference assumptions by randomization having a sufficient sample size allocation, concealment, and double blinding. And the ICH guidelines nicely articulate what the purpose of blinding is in clinical trials – by blinding and masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment allocation of subjects and the attitudes of subjects to those treatments. Another way that we can think about causal inference and the treatment and the effects that it may have is by putting it into a diagrammatic format where we have our, I'm not sure if you can see the mouse. You can see cause and effect. And one of the things we're looking out for is things that might confound our cause and effect. So that's what a basic causal diagram looks like.

(00:45:28):

And if we then think about what actually happens during treatment, we can flesh it out a little bit further to this causalmodel for treatment where we have treatment might get offered, treatment might get received, and has a clinical outcome. We have confounders that may be influence that those that might seek treatment and the responses when they receive the treatment, they might have blinding effects and they'll have an expectancy and expectancy and blinding will interact. And that will also affect the clinical outcome. In randomized controlled trial, what we do is by randomization, it breaks the backdoor pathway between the confounders and the treatment offer. So that's really nice and it's the beauty and power of randomization that it simplifies our causal diagram. And in the case where the trial is truly blind, the black arrow here between receiving the treatment and blinding becomes nullified.

(00:46:35):

And what we essentially get isn't very nice, simple... In a well-blinded RCT, we get a very nice simple causal pathway between our treatment, treatment being received, and there being a treatment outcome. And there are no backdoor paths or confounders in our treatment response. And so the intention to treat effect is the pathway between treatment offer, treatment received, and the outcome. And then what we can see is that the placebo treatment would be C+E, and the active treatment and with the blinding would be C+E+A. If you subtract the two, then you can, what statisticians would say is you can identify the treatment effect.

(00:47:20):

When, however, our blind gets broken, we can formalize the logic here. And our placebo treatment with a blind is C+E. And our active treatment with no blind is C+E+A+EXP. And what you realize is when you try to look at the difference between those conditions is that you cannot distinguish the treatment effect A from the expectancy blinding interaction. So the treatment effect cannot be identified in a two-arm trial with a broken blind. So we cannot distinguish the treatment effect from the placebo expectancy effect. And if we go back and we consider that scientific standard again to establish could-

Speaker 2 (00:48:08):

[inaudible 00:48:09].

Dr. Suresh Muthukumaraswamy (00:48:10):

To establish a drug's effectiveness, it is essential to distinguish the effect of the drug from other influences such as spontaneous change and the placebo effect. So it is essential to distinguish the effect of the drug from other influences such as the placebo effect. But quite clearly the formal logic

demonstrates that we cannot when our blind is broken. It gets more complicated than that because actually what I've put in the diagram is quite a simple thing. The treatment as the previous speakers alluded to, actually the treatment's pretty complicated. And this A gap is actually a pretty complicated evolving temporal sequence of interactions between the patient and the therapist. And actually if we'd able to see the video that I'd played, you would've seen actually that the therapist would be treating or interacting with a patient who was in the placebo group quite differently to how the patient in the active group was getting. So they are getting differential therapy and this violates the consistency assumption. So it's unclear that therapists are always treating the patients in the different groups the same. So this is another violation of the causal inference logic. This can lead to differential therapy and that will lead to differential therapeutic alliance. And we know that therapeutic alliances is one of the largest predictors of clinical effect in psychotherapy. The content of psychotherapy therapies as well can be a little strange if you're in the placebo group because often they invoke reflection on mystical experiences, et cetera, et cetera. And in the case of non-interference, if we zoom out of it and take our causal diagram, but now we think about it maybe like a block design in a single trial or maybe a cross trials, what we get is actually contamination effects that can actually occur across trials because the lack of blinding now lets a gateway in for one trial or one patient to contaminate other patients. And we articulate this in this paper here.

(00:50:25):

And I think Michael Pollan's getting quite a lot of advertising today. So here's another picture of him and Tehseen Noorani coined the phrase 'the Michael Pollan effect.' But what you can have is the perceptualizing accounts of one patient maybe on social media or through the various media then can get amplified and actually contaminate or have an epidemiologist would call a 'contagion effect.' And these contagion effects can cause intra and inter-trial contamination of our treatment response.

(00:50:59):

And some of the examples of violations in the non-interference assumption might be group therapy, participants forming integration groups. You might have this way that you're sampling through maybe snowballs or self-selection. And of course you've got media hyping concurrent trials going on in the background there. So these can all lead to violations in the non-interference assumption. One of the things what we might want to think about is where the treatment effects should be stable to this expectancy and hype contagion that can happen. So I think these authors will be speaking tomorrow and they'll argue that when the bubble bursts we'll reach some kind of plateau. But in our view, this ignores contagion effects. And so it's entirely possible that the placebo and treatment effects where our treatment effects can be so influenced by the media landscape and the is that, they might bounce around the size of the treatment effect might bounce around with the political and social landscape.

(00:52:07):

And so how do we know that psychedelics will still work or work as well when the media landscape perhaps sells on psychedelics, we may end up in a situation where harm gets amplified. And I think typically when medical interventions are approved, there's the assumption that they're going to be stable over time. So we articulated this in this quote: "There's been argued that there's no pragmatic need to separate expectancy effects from true treatment effects in psychedelic medicine. However, such an approach creates the unusual situation where the efficacy of a medical intervention is unstable over time and potentially at the whim of a social zeitgeist." And if I was the person who was paying for psychedelic therapy, like an insurance company or healthcare provider, I would be concerned to know that my treatment effects post-approval are going to be the same size as what they were at approval time. Otherwise the economics is not going to make sense.

(00:53:03):

So just to summarize some of these issues, you have violations to the interference assumption, lack of ability to identify treatment effects, and you have differential therapy. And this disappointment and expectancy effects can lead to effect size overestimation. One of the things that clues that you can see where unblinding is probably happening in trials is actually if you look at the control groups and you have these muted, and I'm not going to name the sources these papers, these just typical examples, but what you can see is these pretty small placebo responses. And often in the placebo group, and this is probably because the placebo group have worked out, they are in the placebo group. And you can compare these to placebo responses for well-blinded interventions where the placebo responses will typically be much larger like two or three times larger than what you would see here.

(00:53:57):

And that's a clue for the reader that probably some unblinding is going on. And once you have an unblinded RCT, you might just say, well, it's now essentially an open label trial, but it's not actually because in an open label trial, participants fully expect to get the intervention. Whereas in a double-blinded RCT patients are like, "Am I getting it? Am I not getting it?" And given the proposed importance but never verified importance of set and setting, it's not given that the de-blinded RCT equals an open label trial equals real-world treatment. That's a big assumption.

(00:54:38):

And one of the things I'd like to stress in this talk is that the expectancy is shaped by the information given to participants. What are we actually telling people about the trials and what answers are they being given back by the research team? And this is all of course given information sheets and advertising that we almost never see. You see publications, but you almost never see the information. This is really important because it's going to shape the clinical response when a trial becomes unblinded. And if you can't see this information, it becomes really almost impossible to actually interpret the data because you don't know what the participants know about the format of the general trial itself. Patients ask questions and what answers are they being given? So I'd suggest that we need to be much more transparent about providing this information to readers. And we know stunningly little about what participants think about having their expectations met or not when they're engaged in a psychedelic RCT. And this certainly needs much more detailed investigation.

(00:55:45):

I would suggest that measurement of the blinding should be mandatory. Readers and evaluators have no idea to the extent of the problem. There's various ways to do this, but really it depends on the design of the experiment. And there are various designs for these things, and you can look these up in our source paper and some of them are good and some of them bad, but I don't really like to think about design too much because we think about that and what should be appropriate placebo a lot. What we don't talk about is how the design interacts with the patient-facing materials. And that's what I think we really are not addressing as a field. And we need to carefully consider things like concealment options, information and trial design in tandem with the de-blinding measurements. I'll skip over that one and just come to a conclusion that de-blinded trials can't distinguish between placebo and treatment responses and interference consistency and contagion effects contaminate probably all of the existing psychedelic RCT data.

(00:56:52):

In my opinion, de-blinding measurement should be mandatory. Actually providing readers and things like information sheets probably should be mandatory. We should be thinking about trials more holistically just than what is the placebo and what is the trial design, but more around what the information given to participants. And just to close off, I'll let you read this quote from Sidney Cohen,

one of the great researchers of the first wave of psychedelic research and who I have turned out have basically ripped off his ideas for the last couple of years, but you can read the quote. But he says here, "The difficulties in others of running psychedelic trials, the reason why decisive tests of the efficacy of LSD has not yet been performed. These problems are great, but surmountable. Hopefully this investigation will be done one day." And this quote was in 1964. We are now 60 years later and we have not done this trial yet. And that will be the conclusion of my talk. Thank you very much.

Susan Winckler (00:57:54):

Well, I have to say since you're joining us from February and the next morning, that was just fascinating and so helpful, Dr. Muthukumaraswamy. Thank you for joining us and grounding us in some of the important information about communicating with participants and just some important dynamics. We'll let you step away. We'll turn to our next speaker and then we'll invite you back for the panel discussion in just a bit. So let's turn to our second speaker of this session who is Dr. Franz Vollenwieder, who's the Chief Psychiatrist and Co-Director of the Center for Psychiatric Research at the University of Zurich. Dr. Vollenwieder, I'm going to turn the program over to you. Dr. Vollenwieder, we can't hear you.

Dr. Franz Vollenweider (00:58:56):

I'm sorry. Okay. Is this-

Susan Winckler (00:58:57):

There you go. Yes.

Dr. Franz Vollenweider (00:59:00):

Okay. Thank you so much. It was a pleasure to hear Suresh, which is work I know well, and I'm happy that he took over the highly statistical parts. So what I wanted to introduce today are some thoughts about what we are doing currently in psychedelic research. Also from a practical point of view, what can be done and where do we stay and where should we go forward? Can you go to the next slide please? What I wanted to show you is we have a long history in Switzerland because on one hand, LSD was discovered in Basel. And then later on in the 60s, Hoffmann also discovered and synthesized psilocybin, which is used now as 'quasi standard' in the psychedelic research. So since the 50s in our hospital research is going on, but from all different kinds of perspective. We started in the 50s and 60s, there was the idea that these drugs can be helpful in learning about the brain chemistry of psychiatric disorders such as schizophrenia.

(01:00:14):

But happily, Bleuler, who coined the term 'schizophrenia,' said, no, this is not a schizophrenic patient, it's a volunteer on this drug. So from that moment on, also a number of initial studies were done in Switzerland into depression, particularly using LSD. And later in the 60s and 70s, they used also psilocybin. Now, at that time, people were very driven by psychoanalytical thinking and the drug was embedded in the psychotherapy and not the other way around like it looks today that you use the drug and you minimize psychotherapy. So it was quite another perspective. So in the late 70s, beginning of 80s, there was a group at the hospital, they were interested in the common denominator of all the states. Psychedelic is just a small part. They started hypnosis, meditation, sensory overload, sensory deprivation. And that has led to the 5D-ASC Rating Scale, which is widely used in many of these ongoing psychedelic studies over the years.

(01:01:38):

When I joined the institute in beginning of the 90s in 92, we started to revise this rating scales to refine them. And just recently that came out a very brand new form. It has 13 dimensions that try to catch the acute experience independent of the user. So the other thing in Switzerland, which is special and we can learn a lot is that we are allowed to do so-called 'compassionate studies' with psilocybin and LSD. From these psychiatrists, we can learn about the therapeutic integration and how they make progress with different kind or forms of psychotherapy. But these are only observational studies so far. Now, when we started, we were also very interested to understand, in particular, the biological mechanism behind psychedelic drug action. And one of the first breakthrough 'quasi' was when we sorted out the many receptors that may primary involved in the psychedelic experience and it turned out in the beginning of the 90s that the serotonin 2A receptor is responsible.

(01:03:09):

This is important because what we try to understand is going from the pharmacology to the psychedelic experience. And what you can see on this slide is on the left side we manipulate the receptor. We study using new imaging – fMRI, EEG particular and the positron emission tomography – to understand this relationship of receptor occupancy by a drug, changing in connectivity between areas, and linking that as a correlate on one hand with the subjective experience and on the other with specific brain functions such as memory, planning, emotion regulation, and all these different kinds of things. And we made quite progress. And it is quite sure together with many ongoing research, for instance, with Gitte Knutte in Copenhagen, that the amount of psilocybin that sits on the 2A receptor correlates with the change in the psychological experience and, in our hands, also with the network and the connectivity.

(01:04:35):

So why is that important? This is important that we think that you cannot manipulate this kind of biological relationships just by mental activation and expectation. So that would be a big step forward if we would come up with the biomarkers. Can you go to the next slide please?

(01:05:06):

Yes. As a example, I wanted to take three or four studies to look into what's really challenging at the moment. So a number of studies, like the study on the left corner who used a waiting list from the Rowan Griffiths group, showed that psilocybin rapidly reduces symptoms in major depression and in therapy-resistant depression, is large study from Compass showed using three different doses as a relatively fast onset and it endures over weeks. And then the most new study from the Usona Institute in MDD showing also that psilocybin compared one dose with placebo, which was an active placebo niacin, shows a rapid decrease in symptoms. And our own study we used inactive, quasi, and inert placebo, was really sugar, compared with psilocybin. What you can see is then it endures. We followed that, for instance, our patient for three months. The Usona study also for a few weeks and a long time has been suggested that this symptom reduction endures two to three, to four to five months. So it's difficult to say what's the mean. I would say it endures about two to three months.

(01:06:49):

What does this implicate? It shows that it's very complex to give a second dose after the initial dose. When should you start the second phase to test, for instance, different doses or in a crossover study? First placebo, then the active dose or the active drug and then placebo. So at the moment, all these designs look like phase I studies. And what we also see is that, for instance, in therapy-resistant depression, there's a relatively small decrease in symptoms depending on dose. In this case, 25, 10, I think one milligram in the Usona study, 25 milligrams in our study was a moderate dose about 15, 18 milligrams. But the difference you can see is on the right side we have major depression, medium,

moderate extent of the symptoms, the therapy resistance had a little bit higher symptoms probably, and there are different reaction patterns.

(01:08:03):

So what is the question? The question is, what dose is really needed? And then you look at those comparisons in the study of Goodwin, then you see that 25 milligrams and 10 milligrams, they really bring down the symptoms. One milligram also had a slight effect, which could possibly be the placebo effect like in the other studies on the right side. So what was clear that blinding was broken in all these studies and reported in the US on a study very nicely. Unfortunately, we haven't really studied efficacy of breaking the blind, but we had studies in the placebo group, the therapeutic alliance, the relationship between patients and therapists to find out how people who get really a placebo react.

(01:09:05):

And it was interesting to see that only four patients went worse over the first two weeks, but then almost went back to baseline because they were integrated in a supportive psychotherapy. Not in a classic psychotherapy, but in a manualized way, how we prepare and integrate this patient. So what's the problem of all these studies when you break the blinding or the masking? As Suresh said, you cannot undermine the cause-effect relationship. It's a threat to the validity of a study. Next slide, please.

Dr. Franz Vollenweider (01:10:03):

I don't have to go into this because Sue has showed so much. But what is interesting is that we have a placebo response. You see that on the right side, and that also includes the regression to the mean. So we do nothing with the patient. You do not treat them. So the symptoms can go in some patients starting sums up and you have a regression to the mean. There's spontaneous remission and there's also response biases. And then you have the so-called 'placebo effect,' which depends markedly on the expectancies, the conditioning, the suggestibility, and the belief system of the patients. So it's the whole package. You want to really tease out in a placebo versus drug study, the placebo effect, you would have to do a study where people are not treated that you see on the upright corner. To uncover this would take an additional no treatment control group. That is ethically difficult.

(01:11:09):

You have to think about how you organize that. But the most true threat to the validity of the study is breaking the blind condition. And the other is the influence of expectancies. How do you control the efficacy of this. And the recipe or suggestions that came out of a number of recent reviews on that problem is we have to assess blinding, blinding efficacy using a parametric scale. For instance which in our case where you have yes or no, and everything between the probability we can bring into a kind of correction into the analysis. And the other is the assessment of the expectancy. There are rating scales here like the CEQ or the sets. Well-established scales is not just the in-house made rating scale. You have to compare these things with other studies. Next slide please. So what is a little complicated, but it's just a practical thing how it goes in a clinical trial.

(01:12:36):

The expectancy starts also with the study advertisement and the patient information and then in with the inpatient screening. So the assessment has to start relatively early, maybe before you give the drug. It's also very important how you inform the patient. And here what comes here in is a certain, on the one hand selection bias, how you sample your patients. Maybe you should take only drug naive or you should really know and understand the previous experiences and you say there has to be in a certain period where people are not allowed to take drugs or you exclude them. But this brings into all different kind of biases. What I want to show here is also is that we found in our studies, we have done a number

of drug response studies using imaging or not imaging or EG, dose is the most responsible driver for the acute drug response of the psychedelic experience, but it's certainly shaped by the number of non-pharmacological factors.

(01:13:49):

You see on the left side, we have statistics done in about 300 to 400 single trials double-blind and we see that personality traits has an effect, previous experience, age. And particularly, and this is interesting, emotional regulation. People that can accept their emotions, they drive into a positive experience while, for instance, people that suppress emotions, they have rather a negative experience. Now, what's the mechanism that people suggest nowadays is that the psychedelic experience is important for the outcome. But you could also say that the drug level is the primary thing and the psychedelic experience is not that important. So the assessment of this expectation has to go time by time. Sauti's idea that the mystical type experience is the main driver is a question and it's a question because the measure assess alterations itself, self-experience, and alterations to the emotions that led us to use specific neurocognitive markers like emotional regulation and paradigms for social recognition or social interactions. And empathy measures which are more similar altered that can be influenced by psychedelic drugs. The question is how long does the change last when we give psychedelics, when we do baseline measures?

(01:15:39):

Next slide please. You can see these on this slide on the left side, 25 milligrams of psilocybin gave this reduction. 10 milligram in another open-label study also made a marked reduction and explained a lot of the effect of the outcome. Now, what is the best dose? The question of the workshop is what kind of dose? And you see, we or I would suggest that high dose compared with a medium dose and then a low dose is a certain approach. And for the low dose, you have to have numbers. And we have tested very low doses, one, two, and three milligrams. With three milligrams people start to say, "Oh, there's something psychedelic." 66% of healthy volunteers say, "Oh, there's something going on." So you have to mask somehow the effect and maybe you randomize the trials, you use three arms or only two. But this also has to be explained in the information how we inform the patient.

(01:16:56):

Next slide please. Now we can improve that and so far that we look at potential biomarkers, immunomarkers and stress markers. We have seen are altered by psychedelics. So we have baseline measure and we do that two days later, after two weeks. We have seen that emotional regulation, rumination, self-processing task are nicely stable modulators from psychedelic drugs. You have to test a little deeper to dose dependency and change in connectivity and such are potential neuroimaging markers or paradigms for emotion regulation. Next slide please. In fact, what we have seen is that in our depressed patient that giving one dose of psilocybin really alters emotion processing. Now we try to understand how this is linked to neural activity and changes in connectivity. And there are some really promising markers that can add a lot to the clinical observation. Maybe the last slide please.

(01:18:13):

Just one more then I can take it together. Oh, no one back, sorry, excuse me. Just on the left side, there are different kind of active placebo. Here we have to think about what do we want to mimic. If we take amphetamine-like stimulants or we modulate emotion and don't hit the psychedelic spectrum of all these experience, we have a chance that we can reduce the expectancy effect. And on the right side there are different designs and rich designs where we can study, for instance, how is the drug embedded in psychotherapy? We split the patients, one has only 7 hours, the other get the 14 hours to all different kinds of enrichment things. Next slide please. And that may be the most important. As I told

you, blocking the 2A receptor we have shown that washes out, decreased all the psychedelic symptoms, next slide please, in a dose dependent manner.

(01:19:20):

But it also activates the glutamate system for those who are not in field and drives neuroplasticity. And now many people say, we don't need 2A effect, we just need the glutamate effect or let's say the neuroplastic effect. And it seems that psilocybin does independently of activating the 2A receptor just to stimulate neuroplasticity. But how is this neuroplasticity linked to symptom improvement? That's a question mark. And our own animal studies give a hint what could be altering, for instance, deep in the regulation of fear and emotions, but this has to be sorted out. So one last slide please. One thing is next is that we do pre-treatments.

(01:20:17):

What we could do is we give the blocker in different doses before we give the active psilocybin down to a very, very low dose where we have the possibility on the one hand to study the impact of the psychedelic experience and the impact of different doses and combined with biomarkers. So that's more or less what I wanted to show you is that it needs a deep thinking about what's a real active placebo, what do you want to study? And when you go deeper into pharmacology, really what aspects of the neurochemistry and the link between neurochemistry and receptor occupancy and the outcome has to be established to help to control the influence of expectancy on the therapeutic effects. Thank you very much.

Susan Winckler (01:21:20):

Dr. Vollenweider that was really helpful and built so well off of Dr. Muthukumaraswamy's remarks. Let's go now. I'd like you to stay on camera, invite Dr. Muthukumaraswamy to come back to camera, and I want to introduce three individuals who we've invited to react to the presentation and help stimulate dialogue here. So in addition to our presenters, I'll invite Dr. Matt Butler, who is a doctoral clinical research fellow from King's College London, with interest in neuropsychiatry, psychopharmacology and non-pharmacological treatment effects, who is currently undertaking a neuroimaging study into the effect of the psychedelic psilocybin in functional neurologic disorder. Then we also have Dr. Michael Davis, a psychiatrist and pharmacologist who serves as Chief Medical Officer of the Usona Institute where he provides leadership in clinical development, medical affairs, pharmacovigilance and regulatory issues. And finally, Dr. Bernard Fisher, a psychiatrist and the Deputy Director of the Division of Psychiatry in the Office of New Drugs in CDER at FDA. Dr. Fisher has over a decade of clinical expertise in the treatment of psychotic disorders, psychoeducation and psychopharmacology.

(01:22:45):

So let's bring our panel on screen and as I go to turn into questions, I'll first say to Drs. Butler, Davis, and Fisher, do you have any questions or anything that you want to probe following up on those content-rich presentations? Anyone want to jump in on a question or an observation to what we just heard? All right. If no wonder, well, Dr. Fisher, you unmuted.

Dr. Bernard Fisher (01:23:23):

Right. So no questions per se. I think the presentations were great. One remark, just to kind of summarize where we are, it does seem that this is a rare spot we're in where we have a drug class where we have so much human experience and yet we know so little about these drugs and why they work, if they do. The positive effects that we've seen. We don't really know what causes that, what's necessary and sufficient for that. Is it some kind of a serotonin effect? Is it the psychedelic experience

itself? Is it the integration sessions that happen afterwards? And I think identifying what is really the active component in this paradigm will help us come up with better designs and better controls.

Susan Winckler (01:24:07):

And building on that observation, it strikes me as was mentioned, there's a lot of media coverage. And so Dr. Butler, I want to turn to you. Can you tell us a bit about how media coverage of psychedelics may have impacted trial participants' expectancy? And then how does that affect researchers' ability to measure treatment effect?

Dr. Matt Butler (01:24:35):

Brilliant. Yeah, thank you so much for the invite to speak today. It's great to see so many people here coming in from different perspectives, which I think is really key in a complex field like psychedelics. I think that the unblinding and expectancy effects have been really well covered by the previous two talks, which are fantastic. And so just to build on this idea of what expectancy is in clinical trials. So I work in psychedelic trials using psilocybin and I've been in different kind of neuropsychiatric conditions. And participants in these trials come where they've kind of internalized expectation about what therapy is, about what psychedelics are, about what they might get from being involved in a psychedelic trial. And these expectations, these are internalized ideas come from lots of different aspects of the world. So from people's own beliefs, but also from the media. So I think that the patient information leaflet were mentioned as one source of influence of expectancy.

(01:25:34):

I think that's true, but I think that there's much broader social cultural influences on these expectancies. I think when we're in a session with the patient like we are now, when I'm constantly dismayed of the sort of narratives that psychedelics are these wonder drugs and they're going to cure everything, which of course we know that's not true. But people are reading these stories, they're seeing these television documentaries, and that's bringing them to these trials with often an inflated sense of what might result from the trial.

(01:26:03):

And as we've heard, the unblinding effects can then lead to people being either very, very happy with their allocation and the expectancy effects being going along the track they thought it would, I've got this wonder drug I'm going to do better. Or this massive disappointment, I've had this depression or whatever for so long and I've missed out on the opportunity to get to wonder drug, what am I going to do now. And so this artificially inflates the difference between the control arm and the placebo arm. So I would caution, well, I would advocate for caution from such narratives about psychedelics trying to tread the sort of middle path between recognizing that they may be useful drugs and medications alongside therapy for some people, but also acknowledging that they're not going to be a sort of miracle cure all.

Susan Winckler (01:26:49):

That's really helpful. And I think hearkens back to Dr. Muthukumar Swami's thought about what information is provided to participants. And then as you noted, many of these participants are actively seeking an answer, as many are in clinical trials but helping to better help the participants better understand the dynamic in which they're operating. Dr. Davis, we haven't heard from you yet, and so I'll invite you to unmute. And what would you add to the comments we've already heard about researchers in designing the clinical studies to minimize sources of bias, such as unblinding? What would you want to say about that?

Dr. Michael Davis (01:27:41):

Yeah, sure. Yeah, thank you so much for the invitation to participate in this important forum. So I definitely took a lot of notes during the excellent presentations by Dr. Vollenweider and Dr. Muthukumar Swami. And in terms of developing the study, this is something at Usona we take very seriously and we really appreciate the guidance from the Agency, which I think is very reasonable. And I also appreciate Dr. Facchioni's comments about that we're sort of entering an uncharted territory with this and doing the absolute best we can to address these important issues. So I think basically our approach is to do as much as we can to characterize these effects. So we agree with using blinded central raters for the primary endpoints, raters who don't know what visit number it is and don't know the design. We agree with administering the blinding questionnaire to participants, facilitators as well as the site raters as to their guess of the treatment and the competence in their guess because they may have some degree of uncertainty.

(01:28:59):

And we like the approach of administering it after dosing, but before discharge, because if you were to ask let's say six weeks later or something like that, then participants would be kind of integrating the efficacy, the effects on their depression into the guess. And we are really focused on their experience guessing what the dose experience was. Also, expectancy questionnaires, we think that's an important thing to characterize and our approach is to assess it multiple times because we acknowledge the potential contributions of information sheets and the media and so forth. So we choose to assess this before the preparation activities, at preparation activities and before dosing and also the day after dosing to assess pre-treatment, positive expectancy, effects of the preparation on expectancy, and post-treatment expectancy, whether it be positive or negative based on their experience.

(01:30:07):

And we also are doing intensive training of the facilitators because specifically not to discuss any details of the dosing session or integration sessions, and also to not discuss any sort of guesses with participants or other staff. And sometimes participants may ask facilitators, and it's important just to not give any sort of comment about that and to just overall treat all participants the same regardless of whatever treatment that the facilitators might guess they received. And we also choose to use a thoughtful design of information sheets, materials, facilitator training to minimize those contributions into expectancy to take a more neutral tone and just be as neutral as possible and not exaggerating the potential benefits based on literature or anything like that. Does that address?

Susan Winckler (01:31:16):

Yeah, Dr. Davis, what great kind of practical parameters that you're describing in thinking through how you do this and some of the experience there. So very, very helpful. But let me turn back to you, Dr. Fisher. We heard that excellent overview and explanation by Dr. Facchioni of the guidance document released last year, which has a variety of considerations for designing adequate and well-controlled clinical studies. Is there anything from the guidance that you would want to highlight as we think about this component of today's discussion?

Dr. Bernard Fisher (01:31:59):

Sure. Yeah, I think it's really important to highlight that as opposed to other development programs for standard drugs that we look at. It may be that for psychedelics for development programs to answer a lot of these questions, that you're going to have to have different designs within a given program. So instead of having just two placebo-controlled studies, it may be the case that we would want to see a placebo-controlled study to really characterize the safety of an intervention, but then we might want to

see something else for the second adequate and well-controlled study where you compare, do something like a dose-response study like has been mentioned in some of the presentations today. We might want to see something with an active control where we wouldn't necessarily be looking at safety per se in those studies. We would look at safety, but it wouldn't be primarily for that. It would be primarily to look at an efficacy where there would be less chance of unblinding maybe.

Susan Winckler (01:32:58):

That's really helpful. So I think it's inviting that exploration of how to address these issues. So we do have time and we're getting such active engagement with the audience, which is wonderful. I want to ask a question, and I invite any of you to unmute and engage. And this was talked a little bit, but are there telltale signs during the clinical trials with other classes of psychiatric drugs? Are those less problematic than the more florid signs for psychedelic drugs in terms of unblinding? And a couple of you mentioned this, but let's probe a little deeper on whether the telltale signs with other psychiatric drugs, are those less problematic than what we see here? I've got a lot of unmuting. Yep, Dr. Davis, you go first and then I've got Dr. Butler and anyone else jump in too.

Dr. Michael Davis (01:34:02):

Yeah, I think this is an excellent point, excellent point. And I do think this is an issue with many psychiatric drugs or even other classes of drugs that the adverse events or appreciable psychoactive effects can lead to some degree of functional unblinding. I think psychedelics, it's particularly because of the intense acute psychoactive experiences, I think it's a very salient issue. But I was kind of thinking through Dr. Muthukumaraswamy's presentation about how I really liked how he broke down the model of the different contributing factors into the overall model of the treatment of effect. And I was kind of thinking that this would be useful to think about for other psychiatric drugs as well, and not to just make it all about psychedelics, even though it is important for them because many psychiatric drugs will have effects that people will be able to notice

Susan Winckler (01:35:01):

A great point that we can learn in many different areas and then use that to improve our research across the space. Dr. Butler?

Dr. Matt Butler (01:35:11):

Yeah, thank you. To be honest, I haven't got that much to add actually from what Dr. Davis said. I agree, I sort of see myself as a bit of a centrist in this kind of debate. And I do want to temper over high, but also I think that we should acknowledge that there is nice evidence that psychedelics could work, and therefore, I don't think that the fact that there are these complexities should mean that we treat evidence for psychedelics in a categorically different way than that we do in trials for other medications, particularly psychoactive medications. So perhaps it could be seen as some spectrum where the challenges are more amplified, but they're not unique per se. I also think that psychedelic trials, are they more akin to psychological therapy trials? What are we actually measuring here and what can we learn from the way that we gather evidence from, for example, psychological therapies that we might not do so much in drug therapies, and can we kind of combine these methods of gaining evidence in order to try and inform our decisions about whether or not these will be clinically useful therapeutic interventions?

Susan Winckler (01:36:16):

Really helpful. Dr. Fisher.

Dr. Bernard Fisher (01:36:18):

Yeah, one thing to add that, I don't have data about this, but just thinking through things, we definitely have functional unblinding with other drugs that we test. And it may be the case that if you're receiving a drug and you have an adverse event, you can tell that you're getting an active drug. But what's not really clear to me is the amount of placebo unblinding that might be in some of these other studies. If you're receiving placebo for let's say a serotonin reuptake inhibitor, you may not know that you're getting placebo per se, but I think in the case of psychedelics, if you get a placebo, you know you didn't have a psychedelic experience for the most part. So I'm not sure how that compares and if that's important with maybe some of the disappointment effect we heard about earlier.

Susan Winckler (01:37:01):

Yeah, yeah. Which leaves us, we have about a minute and a half left, so I want to provide, yes, I was just going to say to Dr. Muthukumaraswamy and Dr. Vollenweider if you would like to jump in and say anything. Suresh.

Dr. Suresh Muthukumaraswamy (01:37:16):

Yeah, I'd just sort of endorse some of the points that the other speakers like Michael have made. And I'd say if you can measure the unblinding and get maybe closer, so your unblinding rate is maybe not 99%, but down to like 60%, 70%, then you could potentially start to stratification analysis and look at only those participants where the NC, whether your treatment effects still exists post-stratification. And that would start to provide evidence that requires us to get our designs a bit better so that we're a little bit less unblinded because you can already do that with antidepressant trials, for example. So this would be a move in the right direction.

Susan Winckler (01:37:56):

Yeah. So better and perhaps not perfection. Dr. Davis, is it all right if I go to Dr. Vollenweider first and then turn to you? Great, Dr. Vollenweider?

Dr. Franz Vollenweider (01:38:01):

Yeah. What we observed is that lower doses are also quite expected in research setting as in clinical practice. And that I think the problem to blind these kinds of doses is less problematic than this full-blown dose people speak about. And that would be that much important. But in our hands, I don't believe that this is needed, but it is my belief system because we work mostly with therapy into emotional regulation that goes through emotions and breakthroughs and all these things and not spiritual experience and all that stuff. Maybe nice and transform you into another dimension. But from a clinical point of view, what patients say, and these lower doses we can repeat after two months, after three months, the high dose, we don't know how long they last and all these things in terms of if they are very effective to have a second phase.

(01:39:12):

But I think at the moment we are well when we just do one phase studies and then switch to two phase studies where for instance we take people that do not react to placebo and randomize them again to placebo and drugs and with the drug people we do the same. So it's a more enriched kind of design that has several phases, but it's very expensive. It's a lot of work. Thank you.

Susan Winckler (01:39:44):

But an intentional design as you've all spoken to. Dr. Davis last word because then we need to go to a break.

Dr. Michael Davis (01:39:50):

Okay. Real quick point. This is something I also thought during the presentation. One point that I haven't really seen discussed as much is just the durability of the effects say after a single dose. That if you have sustained long-lasting benefit after a single dose, how likely would it be that functional unblinding or expectancy effects alone would be expected to produce the long-lasting benefit from a single dose. And I think this is something that studies are looking at, studies have already been conducted, can help inform that as another point in terms of considering the effectiveness of the drug.

Susan Winckler (01:40:32):

And you previewed, we're going to discuss durability later today and so appreciate that. I'll have everyone join me in thanking our speakers and panelists for this morning. We are going to take an eight-minute break and so we will be back at 10 minutes to the hour. So take a moment, stretch your legs, refill your coffee, answer the email you've been meaning to respond to all day and we will be back shortly. We're going to talk about dosing of psychedelics at 11:50 AM Eastern time. Thank you all.

Dr. Michael Davis (01:41:05):

Thank you.

Session 3: Dosing

Robert Barrow, MSc, Chief Executive Officer & Board Director, MindMed
Guy Goodwin, DPhil, Chief Medical Officer, Compass Pathways
Berra Yazar-Klosinski, PhD, Chief Scientific Officer, Lykos Therapeutics
Peter Hendricks, PhD, Professor, Department of Health Behavior, University of Alabama Birmingham
Jennifer Mitchell, PhD, Associate Chief of Staff for Research and Development, University of California, San Francisco
Martine Solages, MD, Clinical Team Lead, Division of Psychiatry, Office of Neuroscience, Office of New Drug, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (01:48:31):

All right everyone, welcome back. I hope you had the opportunity to refresh and recharge, and we are going to settle into our next session of the meeting. In this session, we'll hear about three different products and the dosing considerations for those, and then we will have another reactor panel discussion. So we are going to jump right into content, and I invite Mr. Robert Barrow, who's the Chief Executive Officer of MindMed, to join me on screen. Let's kick off session three and have a presentation about dosing considerations for LSD. Mr. Barrow, would you take it away?

Robert Barrow (01:49:06):

Terrific. Thanks so much, Susan, and thanks for hosting this event. It's really exciting to have an opportunity to in front of a broad audience and a public audience talk about some of these important considerations in research. And certainly there are a number of approaches that different companies and researchers and academic groups have taken as we approach this drug class. I'll just start by, if we

can move on with, of course, we're a public company, so have a disclaimer that we have to put up in front of everyone. Here we go.

(01:49:41):

So we as an organization are developing a pipeline of products from this drug class, from the psychedelic drug class, but really two distinct approaches. And the one that's probably most relevant for dosing discussion is our lead product, which is MM-120 or it's a LSD D-tartrate, which we're developing in generalized anxiety disorder and just reported phase 2B results in December of last year.

(01:50:04):

We're also developing the R-enantiomer of MDMA for autism spectrum disorder, but there we sort of depart from how we think classically about psychedelics, because the analogy that we like to draw with that program is equivalent to how psychostimulants are used in the treatment of ADHD is how we ultimately view using R-MDMA as a regularly administered product to aid in the treatment of core symptoms of autism spectrum disorder.

(01:50:32):

So we'll focus in on generalized anxiety disorder today and our approach. Again, I think the most relevant to speak of is this roughly 200 patient, 198 patient study phase 2B study that was conducted at 20 sites across the US that we read out the four-week primary results in December of 2023. Briefly just showing a schematic of the study design. I'll zoom out for a second and just talk about the reality of researching this drug class. So there is a constant tension and sort of balance that we have to pursue between the uniqueness, the seemingly uniqueness of the perceptual effects of these drugs and how we integrate that into standard research paradigms, how we ultimately come to valid internal and externally valid conclusions about the safety and effectiveness of these products in hopes of submitting an application to FDA and other health authorities and ultimately receiving marketing authorization. That includes balancing things like safety with the magnitude of the need. We have millions and millions of patients here in the US who could potentially benefit from these products if we're ultimately able to market them. But at that scale, of course the controls around safety that we can impart in clinical trials are much different at that magnitude of rollout in the real world. We also have to balance things like the unique perceptual effects that are associated with this drug class and our product in particular with what actually is a safety risk, what are we actually trying to protect against and how should we go about characterizing that?

(01:52:07):

And then I'll also say from a methodology standpoint, and then again get back into the specifics of our study, when we think of asking research questions and think of how we handle dosing and really important element of how we ultimately arrive at clinical outcomes. We have to think about whether there's a change that's needed because of the nature and the actual effects of a drug or if the standard sort of research methodologies should apply. Ultimately, when we look at this and we make decisions several years ago about how to conduct this study, we decided that really what needs to be done here is a standard drug development approach. We need to do standard clinical trials with standard endpoints and to the greatest extent possible treat patients and our protocol the exact same way that we would treat any other CNS drug. So our study was five different treatment arms, four doses of different dose levels of the active versus the placebo.

(01:53:03):

We gave a single administration and followed patients for 12 weeks and again, we've, to date, only shared results from our topline analysis at week four. Critically important, and again zooming back out into this theme of how do we need to administer these drugs to get to valid clinical conclusions, one of

the decisions we made was that we were not going to do any sort of therapeutic intervention other than administration of the drug. So in many different approaches, there's a pre-treatment interval that can involve things that are called preparation or post-treatment follow-ups that are called integration. And during a treatment session, this could be unique for each drug in the class perhaps. But with our molecule with MM-120, we decided that we're not going to do any assisted therapy or therapeutic intervention. Prior to treatment, patients get a comprehensive informed consent process. That's something that's required of any drug. During treatment, they're under observation by qualified individuals that aligns with FDA's guidance on the conduct of research with this drug class. And then from a post-treatment standpoint, they're just followed. Patients return for follow-up visits and assessments for safety and efficacy outcomes.

(01:54:14):

So what we've done now is then isolate really just to understand what is the drug-only effect when we strip away any other sort of therapeutic intervention and that gives us the truest estimate of the drug's effect. What we saw and we're very happy to have seen is that even when we remove any of those other elements that have been used historically, we saw a drastic reduction in anxiety symptoms as early as can be measured. So some metrics like the Hamilton Anxiety Scale, which is the endpoint in our study, and really the only endpoint that's been used for approval of anxiolytics in the past. We saw a 21 point reduction at the most responsive dose group, the 100 microgram dose group versus placebo, which represented a 7.6 unit change over placebo, which is more than double what we've seen with the standard of care with SRIs and benzodiazepine for instance.

(01:55:03):

So these were statistically significant results at the two highest dose levels. The other thing that will become more apparent as we go to the next slide here as well is that while we saw really remarkable results at the high dose groups, roughly 80%, just under 80% clinical responders, so patients who had a 50% or greater reduction in Ham-A score from baseline, 78% in both the 100 and 200 microgram dose groups. And then in terms of remission rate at 100 microgram dose group, four weeks after a single administration we saw a 50% clinical remission rate, which corresponds to a Hamilton anxiety score of seven or less. Basically means no real anxiety symptoms. What we also saw interesting and relevant to the last discussion as well is that at the 50 microgram dose group here where we actually know that there from the adverse events that were reported that there's even more of a pronounced perceptual effect, patients got less better than they did even a 25 microgram dose group.

(01:56:01):

So while functional unblinding and discussions about this are certainly relevant, it actually very apparently in our study that functional unblinding at least was not the driver of clinical outcomes. One other point I would make to that and relevant to dosing is that functional and unblinding may just be a mechanism to connect pretreatment biases, which can be enhance or amplified by things like extensive therapy or preparation to clinical outcomes. So functional unblinding itself may be benign, but if it is used as sort of a mechanism to connect an amplified expectancy bias to a clinical outcome or a nocebo effect, that's where that becomes problematic. So from our data, we actually didn't see a whole lot of impact of functional unblinding either between the dose groups or when we look at the highest dose group and the comparisons there. So as we think about things like dosing but really relevant to many aspects of the research for these molecules, the perceptual effects are clearly so distinct to this drug class.

(01:57:06):

The sort of florid psychedelic effects, the chain alterations to the senses and mental state are quite qualitatively unique. But the question is, how really unique should our research be and how really unique are they at all? Many other drugs, CNS-active drugs in particular, when we think of things like psychostimulants or the dissociative anesthetics like ketamine and Spravato now that are being used in the treatment of major depressive disorder and treatment-resistant depression, these drugs have quite similar effects. Functional unblinding is a concern. We always have challenges with nocebo effects and placebo effects and expectancy bias in clinical research, but particularly pronounced in CNS research. And then really what we have to ask is do any of these qualitative differences demand a different trial design or different treatment or different treatment of patients in dosing? We ultimately arrived at the view that they don't. And really if we're going to make these changes, the question is why. What specifically are we doing that is going to enhance the validity or the truth that we're arriving at as an outcome from these clinical trials?

(01:58:15):

A little bit more specific to the dosing and of course we've worked very closely with FDA and align around and follow the guidance and the requirements for conduct of these studies. But some of the big questions that do need to be asked, particularly as we think about pivotal studies and the impact on the real world is participant monitoring and the ratio between monitors to participants in these studies. Are more monitors safer? Is it safer to have two individuals monitoring a patient than having one? And why two, why not three or four? And these are really impactful questions both in the complexity of research but also are going to have big real world impact. Monitor qualifications, what specific risks are we mitigating by having certain degrees or certain requirements? And this is not to say that we don't agree with requirements. We certainly do agree that requirements need to be in place to protect patient's safety.

(01:59:09):

There are many other areas of medicine as well, where different degrees and different licenses and different areas of practice require different kind of monitoring and don't always require, certainly don't require a medical degree, but many instances do not require a doctoral degree. Things like releasing patients from dosing. So whether it's our product, MM-120, or any of the other longer acting drugs in the class, or even the shorter acting drugs in this drug class, what specifically are we monitoring and what are the specific adverse events or safety concerns that we're trying to mitigate before a patient can be safely released? And we looked at things like surgery and general anesthesia where patients who come in for a day surgery can be put under, completely lose consciousness, be cut open and have something removed or implanted, sewed back up. And there are very fairly liberal requirements for release.

(02:00:06):

I mean, patient needs to be able to walk safely, but they're released under care of an individual that they bring of a care provider who then takes them home. They certainly can't drive or operate machinery or shouldn't go back to work or make big life decisions. But similar here, what specific changes, what specific psychological or cognitive changes, would represent a return to a point where a patient would be safe to go home after a treatment session? Now in research, it's worth spending a minute on this point, in research there's certainly value for keeping monitoring periods consistent across patients. So with things like functional unblinding as a point of focus, we need to make sure that we don't have one group of patients who are leaving an hour into a treatment session, another group who are leaving 10 hours later.

(02:00:50):

But once we've set some sort of reasonable standard as this is the point when a patient would be safe to leave in the real world, it'd be a tremendous burden in cost on our health care system if patients who are free safe to leave after six or seven hours are required to stay in the clinic any longer. So how can we develop research methodologies and ways to monitor these symptoms and arrive at rational conclusions for when a patient would be safe to leave?

(02:01:18):

A little bit venturing outside of this, but it does have an impact on dosing as well, placebo and controls. What is the impact of alternate controls? Things like subperceptual doses or other drugs that have effects that aren't really exactly what we see with this drug class but may have some impact of their own on perception or physiological sensation. So not something that we've seen with other drugs historically, but something that we really need to unpack. From a dosing perspective, if in clinical research we're treating all patients consistently, we try to isolate the variable of does the drug have an impact. And so while there's certainly, again, is a discussion around functional unblinding and expectancy.

(02:02:03):

From a dose administration standpoint, we just need to treat all patients consistently. And by removing things like any therapeutic intervention, we're able to do that. I think it would be particularly challenging to treat a patient who's sitting in a room for a day that's received a subperceptual or imperceptible or a placebo dose. The same as someone who's doing therapy would be treating a patient who's received a high-active dose of one of the psychedelics or MM-120.

(02:02:32):

And finally, from a dosing and a methodological standpoint, how do we characterize the safety and effectiveness of these products? If we had drugs like a long-acting injectable where the PK profile matched very infrequent dosing, I think we can easily get our heads around the exposure matches the clinical effects. But we see things like MM-120 where patients are being administered the drug, the drug is clear from their system, but there's a mini week or month impact. Beyond that, how do we characterize the safety and effectiveness of a product such as that? So I'll pause. I know we're up on time, but thanks so much for, again, Susan hosting us today.

Susan Winckler (02:03:15):

Thank you. And we will be inviting you back for the panel discussion at the end of this session. But let's turn to the discussion of our second substance. And for that, I want to turn to Dr. Guy Goodwin, who serves as the Chief Medical Officer at Compass Pathways to talk about dosing for psilocybin. Dr. Goodwin, what should we learn and understand about the dosing perspectives here?

Dr. Guy Goodwin (02:03:52):

Thank you so much, Susan.

Susan Winckler (02:03:53):

Yes, there we go.

Dr. Guy Goodwin (02:03:54):

Let's go. So we are talking and talk about Con 360 psilocybin just initially disclosures. Obviously I started life in this field as an external consultant to Compass Pathways. I'm now actually fully employed by them. So that's my disclosure. And then in addition, making forward-looking statements, you need to

understand the company a little better. You should go to SEC filings. Okay, I thought a little bit of history was really indicated. If we go back to the first medical era to the 1950s if you like, there were really two ways in which LSD in particular was used. The first was as a low dose psycholytic so-called,which was very expressly said to assist psychotherapy. And subsequent to the introduction availability in North America, Osmond basically took that idea as an English guy and increased the dose and tried higher doses, particularly in patients with alcoholism. And the result of that was a really two different approaches, a high dose and a low dose.

(02:05:04):

So when we're talking about dose low dose is really about this model of assisting psychotherapy. And this was very explicit in the indications and dosage instructions, extremely short compared to what we get now that were published with the Delysid drug by Sandoz back in those days. So we are going to be talking about higher doses. The higher dose model was the one that was adopted when the reintroduction of psilocybin into clinical investigation took place initially by Roland Griffon and colleagues at Hopkins. And they did the first really systematic modern psychopharmacology with psilocybin, extremely informative for all of us. And basically their conclusion was that 20 and 30 milligram oral doses of synthetic psilocybin produced similar dose related positive and wanted effects, but 30 milligrams tended to produce more distressing or unwanted effects. And that essentially formed the framework in which we designed the first trial that Compass conducted in patients.

(02:06:17):

We were also helped a lot by the fact that we've been hearing a lot about placebo effects. It's worth remembering. We are dealing with a drug, in fact, a drug that's the most potent effects on the mind that's ever been described. And really was the stimulus for many of us to see psychopharmacology as having virtue in the first place. And the binding of the drug, psilocin, which is actually the active moiety of psilocybin, is shown on the left here in relation to the intensity of experience. So there's a very clear relationship in whether you occupy the 5HT2A receptor or whether you get a psychedelic experience. And you can see on the right that the actual relationship between plasma psilocybin intensity is quite variable. So there's a pretty definite relationship between receptor occupancy, but we should expect a certain amount of variability in how that's expressed through dosage as you can see.

(02:07:13):

And we'll illustrate why that's important subsequently. Now, you've also heard from Franz Vollenweider that you can do studies using fMRI, which also show very marked brain effects, which are not emulated by placebo. So we've got to deal with the fact that this is a drug and therefore it's worth studying it as a drug and look potentially at different doses. So we are talking, the drug we're talking about is Comp 360 psilocybin, synthetic high purity, polymorphic crystalline formulation of psilocybin. This is developed to GMP standards, if you heard that was important in the introduction to the day. And together with that, we provide psychological support. And the reason we provide psychological support is essentially for reasons of safety. And we think that is a critical component of any research program at the moment, and it will probably be an important component of how this drug gets translated into clinical use.

(02:08:12):

The comprehensive passage that we are putting together includes the nonclinical development program, clinical pharmacology, and of course the efficacy and safety studies specifically in treatment-resistant depression. And we'll talk a little more about the first of the studies that has read out and given us confidence that we have the potential to have an effective treatment. So treatment-resistant depression, the expectations for this group is that they are difficult to treat. By definition, they've failed two other treatments, and so they haven't shown a placebo response to those treatments either. So we

shouldn't expect big placebo responses, but maybe we shouldn't expect big treatment effects either because this is a difficult group. The primary endpoint in this study was determined using a blinded rater, measuring the MADRS, the patient population were withdrawn from any medication that they were currently taking, and that could take several weeks before they were subsequently randomized.

(02:09:13):

It's quite an important point that these patients, for the most part were naive to psychedelics, which had not been true of many of the other studies. And when we designed this study back in 2017, we were trying to anticipate many of the criticisms that you heard in the first part of the day. And among those was the issue of placebo. And our reasoning was that it made a lot more sense with a drug that was not merely unblinding, but in a sense, blindingly obvious that one had had it, that the key thing would be to look at a dose-response relationship. And that meant that there would be uncertainty in the minds of patients about what dose they would have, but they would not be thinking, have I had placebo or active drug? That is not the prior that they would be working with. They would be working with something rather more uncertain.

(02:10:01):

We also were genuinely uncertain about whether or not to anticipate an efficacy signal from 10 milligrams. We knew we wanted to use 25 as the top dose just for the reasons I gave earlier, but we were very interested in whether 10 would work as well. So patients were randomized to receive one of those three doses. As you can see, they were then followed out for 12 weeks. And the MADRS, as I underlined, was conducted by blinded remote raters. We also collected obviously supportive direct data from the patients themselves.

(02:10:39):

What were the results illustrated on this slide? It showed a clear dose-related effect. So you can see that in blue, the 25 milligram effect. In green, the 10 milligram effect. And in the black or gray, the one milligram effect. Several things to note about this. First of all, an extremely early response. So a very fast-acting effect. This has implications we'll come back to in relation to questionnaires about unblinding. Going to week three, which was chosen to be our primary endpoint, which we thought was the longest time one could reasonably expect most patients to stay off any medication that clinicians might want to restore showed a highly statistically significant effect. We used very conventional frequentist testing comparing one and 25 milligrams, and the difference on the MADRS was 6.6 units. That of course compares favorably with most of the antidepressant literature that people are also interested in.

(02:11:46):

Perhaps more importantly, and unfortunately we haven't got confidence intervals on this slide, but if you go to the original publication, you can see this there was a difference not just between the 25 and 1 milligram, but also between the 25 and the 10. And the 10 really failed to separate from the one milligram. So the intermediate dose turned out to be an ineffective dose, certainly given as a single administration. The effect showed durability out to 12 weeks and this durability is a little undermined in this illustration because of the demand we used, which actually worsened the score for patients as they went back onto antidepressants. And so that pushes this apparent curve upwards. If you want to see the true curve, then I refer you to the supplementary data to this paper.

(02:12:36):

So we've talked about a change in the MADRS. That isn't always intuitively obvious to what that means. What about remission, which is perhaps and sustained response, which is the sort of key clinical metric that we are looking for. And you can see that the chances of that are about twice with 25 milligrams

than at either 10 or one milligram out at 12 weeks. And somewhere between somewhere, depending slightly how strict you are in defining the criteria, somewhere between 20 and 25% of patients show this sustained response out to 12 weeks. And we followed a smaller group out for very much longer, and the median time to a subsequent intervention was up to six months. So we've got a fairly sustained response. We don't have yet have the necessary data to be confident about how long it lasts, but that is the first indication we got from a study that we published in abstract form.

(02:13:36):

Adverse events, obviously it's a heavy day. And the treatment of emergent adverse events that was spontaneously reported were mainly on the first day. And obviously, they related over 70% of them resolved on that day as well. The most frequent of these treatment adverse effects were perhaps, as you might expect, headache, nausea, fatigue, insomnia, anxiety. There were no concerns about vital signs, ECG, lab data. And we noticed, of course, that there were treatment-emergent adverse events report of hallucinations. But we think probably that the most effective way of capturing that will be by looking at the ASC scores that we also collected on the day. The spontaneous reports I don't think are really going to do justice to the actual experience that people have. And of course, we can argue about whether these are what we want to see or whether they're unwanted, but they're certainly part of the experience that patients need to be informed about.

(02:14:36):

Finally, there are issues around suicidal ideation, suicidal behavior. I'm not going to dwell on this, but it's an important point that we observed slight excesses of these reports of events in the active treatment arms of 25 and 10 compared to one. Now it's important to understand that there were no attempted suicide attempts and no suicides. What we're talking about here are upticks, particularly on the Columbia suicide rating scale. That has sensitivity, which is important, and it's alerting us to the fact that we have to, in future, be very cautious about how we look at this phenomenon going forward and with larger trials. But at the moment, this doesn't represent a serious suicide signal, but it's something that I think all of us are going to have to be aware of and underlines the need to concentrate at this stage in the development of these drugs on safety perhaps above all.

(02:15:36):

Now, the key lessons we took from this phase two study were that we had a minimal effective single dose, the clear evidence for efficacy of the 25 milligram and this numerical separation from 10 milligram, which we felt gave credibility in terms of the relationship to these arguments about blinding. There was durability of the response to 12 weeks, and we got feedback from the sites that they felt that more than one administration of the drug might be interesting, and especially it might be interesting for the 10 milligram dose. And that has shaped our ideas as we've gone forward.

(02:16:11):

Now, let's return a little bit to this issue of unblinding. I said already that the relationship between plasma dose and experience is very variable, and therefore that implies that the relationship between oral doses and experience is very variable. And this is what we see. This is unpublished data that shows from left to right, different levels of experience measured on the visual reconstruction structuralization score of the 5D-ASC.

(02:16:42):

I mean, this is useful because it really doesn't have a mood component. It's largely about the conceptual distortions and experiences that people have. And what I hope you can see is that you move to more intense experience. You have more and more people who have received the 25 milligram dose. If you look at the people who received the one milligram dose, the majority score of course in the low group

but I think we heard earlier that 70% uncertainty would be good. You can see that even at for this one milligram dose, even at an experience that's below this 12.5 cutoff, 70% of patients received could be confident that only if you had that experience, you could only be 70% sure that you'd had the lowest dose. 30% of people had actually received 10 or 25 milligrams. And as you can move into these intermediate levels, you can see that the uncertainty becomes very much greater if the only data you had to go on was that experience.

(02:17:43):

So the key lessons for the end of the second part of this is the three-dose design appears largely to ensure, if not blinding, then certainly a measure of uncertainty. And that was the feedback we got from the sites. We appreciate that a placebo study is required for a true safety baseline, and we need also to further standardize psychological support to ensure we're clearly measuring the drug effects and not the impact of differential behavior by therapists. And we think there's relatively, there are increasingly interesting emergent ways in which we can use AI to do that, and that's something we're actively working on at the moment. Thank you very much.

Susan Winckler (02:18:24):

Dr. Goodwin. Thank you so much. That takes us through substance two of the three that we want to talk about, and then we will turn to our reactor panel for discussion. So let's turn to our third presenter of this session, who is Dr. Berra Yazar-Klosinski, who serves as Chief Scientific Officer of Lycos Therapeutics, and she will speak about dosing for MDMA. Dr. Yazar-Klosinski, I'm going to turn things over to you.

Dr. Berra Yazar-Klosinski (02:18:54):

Thank you so much, Susan. So thank you for inviting me and giving me the opportunity to present to you all today. So what I'm going to cover today is some of the context that informed the development program of MDMA-assisted therapy for treatment of PTSD, as well as what we learned from nonclinical and early phase clinical trials, and subsequently from phase 3 clinical trials. So the context of the drug development efforts for MDMA is really important to understand because, initially, MDMA was utilized by therapists, most notably by Leo Zef as an adjunct to therapy in the 1980s. And this was prior to opening the IND for MDMA with the Food and Drug Administration. So these reports were published by George Greer and Requa Tolbert, and Sasha Shelgun and Myron Stolaroff. With most new chemical entities, a sizable safety database is needed to ensure that rare reactions and unusual adverse effects can be identified. And generally speaking, post-marketing safety surveillance is relied upon to gather additional safety information on a wider range of patients. With psychedelics, such as the ones we've been speaking of, LSD, psilocybin, MDMA, the situation is reversed. So many of these drugs have been taken by millions of people, and the scientific literature is filled with rare and unusual adverse event reports. So taking into account that many of these drugs are of unknown purity, unknown quality, and in some cases even identity, there's a much larger set of inputs to consider when we're developing the dosing and the risk management plans that are baked into our clinical trials compared to a novel drug that's never been tested in humans prior to the development program.

(02:20:58):

And these clinical anecdotal reports that were previously published, active dose ranges of MDMA were characterized with split dosing, meaning that there's an initial dose taken and then a certain amount of time later there's a second dose taken. And this happens in the same day. And these were reported to be beneficial prior to the start of the development program for MDMA-assisted therapy. Furthermore, single and repeat-dose MDMA, safety and pharmacology studies were conducted extensively. Some of these were funded by the NIH. Many of them were conducted outside of the United States, and these

started around the 1990s. So the development program for MDMA-assisted therapy was informed by over 1500 participants worth of exposure data from independently-conducted research studies. And I just want to make a note that you may not have heard about Lycos Therapeutics before, but we recently rebranded and we're formerly known as the MAPS Public Benefit Corporation, and we were founded by MAPS, a nonprofit entity that continues along.

(02:22:13):

So I want to start out with some key terms. MDMA is an entactogen. This is a subset of psychedelics, and it was recognized in the recent FDA guidance for how to advance clinical trial design for psychedelic drugs in that category. In addition, as I mentioned, the clinical and anecdotal reports had really formed a basis for MDMA to be used in combination with a psychological intervention. And this is currently referred to in the literature as MDMA-assisted therapy. In addition to that, the entactogens are really differentiated from classic psychedelics because of their notable effects for increasing self-awareness leading to introspection and personal reflection and hallucinations are very rarely reported with entactogens.

(02:23:12):

MDMA-assisted therapy includes administration of MDMA during standardized sessions with a qualified healthcare professional, or QHP. And we've described the therapy component of these sessions as a psychological intervention to reflect the intensive nature of these sessions, which go beyond a standard talk therapy session. And they involve the intentional use of the acute effects of the medication. The intention is that these QPS will provide the psychological intervention and they would be carefully selected to convey the qualifications necessary for this role. The mindset of the participant, the social environment, and the underlying experience of the participant all contribute to the outcome of the treatment. So QPS really need to have sufficient expertise to anticipate and support patients during the medication session.

(02:24:06):

So this intervention is intended to enhance the treatment benefit while developing trust between the provider and the patient. And we've intentionally not characterized the risk of use of MDMA without adequate psychological support due to the seriousness of the underlying disease. In our case, this is post-traumatic stress disorder. So we've proposed an acute dosing regimen that reflects what we studied in phase 3 pivotal trials. There are three concepts that are important to understand. First is that taking a set of 3 MDMA capsules, the established name for that is my amphetamine with a psychological intervention equals a single medication session. Second, the medication sessions combined with the follow-up integration psychotherapy sessions, which are intended to allow for processing of the emotions and memories that arise during the medication sessions, equals a treatment cycle. The intention is that the integration sessions would occur during the time in between the medication sessions, which are separated by at least 21 days, and a complete treatment course consists of three treatment cycles.

(02:25:28):

So how did we get to this dosing regimen? So MAPS initially conducted IND-enabling single and repeat-dose toxicology studies in the rat and the dog in the 1980s. We discussed the findings from these studies with FDA and identified the need to repeat certain aspects of these studies. We conducted additional nonclinical studies which are listed here, and the highlight of this nonclinical program are the GLP repeat-dose toxicity studies. And we conducted special neurohistopathology assessments. We evaluated the central and autonomic nervous systems as well as cardiovascular and respiratory effects. And of note, there were no unusual findings in these studies and that expanded neurohistopathology ruled out

any concerns about neurotoxicity. In addition, the program of study was able to establish a NOAEL dose, which is a no-observed-adverse-event-level, with a safety margin in repeat-dose toxicology studies for developmental and reproductive toxicology. The genotoxicity battery was negative and we found no potential for QTC interval prolongation in the hERG study. Now it's really important to conduct these studies because they fully elucidate the safety of the product in a nonclinical or animal or Petri dish type of study.

(02:26:53):

And importantly, we did all of the legwork to really understand if there were any risks that had been missed. So then we wanted to design an empiric dosing regimen, which means that we need to understand what's the relationship between drug-dose and various intrinsic factors, such as weight, when determining what dose to study for MDMA. So this was a phase 1 clinical trial conducted by Dr. Charlie Grove in the early nineties. And the highest dose achieved in this ascending-dose study was 2.5 milligrams per kilogram. We observed that there was a wide variability in subjective effects and pharmacodynamic effects more so than would be expected with a milligram per kilogram dosing approach. And this justified in our development program in phase 2 and phase 3 clinical trials that we should consider a fixed-dosing paradigm that doesn't vary based on weight. It was also important to be able to adjust the dosing, if needed, to assure maximum efficacy. And we also observed acceptable safety results for future research at the time.

(02:28:14):

So we conducted a series of phase 2 PTSD studies, and these were MDMA-assisted therapy where the doses were covered a range from 25 all the way to 125 for the first part of the split dose. And the second part of the split dose was from 12.5 to 62.5. So the key takeaway from this was that we identified the estimated therapeutic bounds after two medication sessions with the split-dosing regimen I just described in six different studies. And we identified, rather than a linear dose response curve, kind of a threshold effect. So you can see that the columns or the boxes between zero and 40 on the first part of the split dose are in one category and the 75 to 125 with the first part of the split dose is in a separate category. So our active dose range was really determined based on standard endpoints for PTSD, and this was what we used to inform our phase 3 clinical trial design. And notably, the second part of the split dose was taken in about 90% of the sessions.

(02:29:32):

The metabolism of MDMA in humans has been well characterized, and most notably we see evidence of non-linear PK, which is better observed at the higher end of the dose range. We also see that there's MDA, which is a psychoactive metabolite, but it is a minor one. And we conducted a series of PK modeling and simulation studies, which identified and supported what the empirically developed dosing regimen had initially put forth. So essentially we reverse engineered what the clinicians were telling us was most beneficial utilizing PK studies. And in addition, the National Institute of Drug Abuse provided us with primary PK data to be able to do these modeling efforts.

(02:30:29):

So our phase 3 clinical trial design consisted of preparatory psychotherapy visits, and then each medication session was an orange box. Participants received MDMA or placebo on three days. In addition to that, they received the integration psychotherapy sessions and our endpoint was at 18 weeks post randomization. With this approach, two phase 3 trials met their endpoints after three medication sessions. And you can see that the lines are starting to separate after the first session slightly, but more so after the second and more so after the third session. And here I'm just showing the PTSD data because it's our evidence of some potential benefit for these patients. And we can see that

overall the participants went from either a severe PTSD level, which is above 35 in the first study, or a moderate to severe level, which is above 28 on average in the second study, and ended up in either mild or asymptomatic range in most cases. And cumulatively, these are the adequate and well-controlled clinical trials that would be necessary to really characterize exposure and the clinical response.

(02:31:59):

So it's also important to look at the effect of the dosing on safety. And so what we saw is that, in general, there were no surprising adverse events found in these studies. And typically speaking, the adverse events resolved within two days. In a small handful of cases, the adverse events extended and were resolved during the week following dosing. In addition to that, there were very few severe adverse events, meaning that they didn't, generally speaking, have a severe impact on daily function. So in summary, we conducted a complete nonclinical program just like any other drug development program. However, those were not necessarily informative for extrapolation of clinical doses. So we really had to learn from the empiric recommendations from clinicians in order to design this development program. We estimated the therapeutic bounds based on phase 1 and phase 2 pilot studies. And due to multiple metabolic pathways that process MDMA and evidence of non-linearity, we couldn't exactly really get to a clear exposure-response relationship that was linear.

(02:33:20):

So we really identified that there was a threshold effect in the dose response. And the phase 3 dosing regimen incorporated a split-dose approach with dose escalation in the three medication sessions. And generally speaking, we saw temporary increases in blood pressure and pulse that resolved by the end of the medication session without treatment and no serious outcomes. So it was really helpful to have the empiric experience with this product prior to conducting the development program. We felt it really improved the efficiency of how to conduct the research. We didn't have to expose more participants than necessary in order to understand the efficacy and the safety of the product. And overall, we're really grateful for, whoops, I wanted to end on my acknowledgements, so we're really grateful for our study participants and their support networks, and it really takes a village to do this kind of research, especially over multiple decades, and we're really thankful to the National Institute of Drug Abuse for providing primary PK data. Thank you.

Susan Winckler (02:34:30):

Dr. Yazar-Klosinski, that was really helpful, particularly your slide where you were talking about basically what you've learned on the dosing consideration. So thank you for that presentation. I want to move us now to the panel discussion. So I'll invite our initial presenters back to the stage. If Dr. Barrow and Goodwin could come back to the stage. And then we have three new faces who I want to briefly introduce as we move into the discussion.

(02:34:58):

First, new face, Dr. Peter Hendricks, Professor at the Department of Health Behavior from University of Alabama at Birmingham, where his current research is on the use of psilocybin in individuals addicted to cocaine, as well as the role of psilocybin in the treatment of chronic pain. Then another new face, Dr. Jennifer Mitchell is a Professor in the Departments of Neurology and Psychiatry and Behavioral Sciences at University of California San Francisco and the Associate Chief of Staff for Research and Development at the San Francisco VA Medical Center. And our final new face, Dr. Martine Solage, Clinical Team Lead in the Division of Psychiatry in CDER at FDA. And so I first want to say to our reactor panelists, do you have any questions or thoughts based on the three rapid fire presentations you just heard? If you do, go ahead and unmute and jump in. Dr. Mitchell, go ahead.

Dr. Jennifer Mitchell (02:36:04):

Thank you very much and thank you to the panelists for presenting today and for sharing your data with the community. I had a couple of thoughts while I was listening. The first was that, as I think all the panelists touched upon when we discussed the dosing of psychedelic medicines, we also need to consider the dose of psychotherapy or the level of facilitation or the number of facilitators that will be coupled with each of these compounds. And that appears to be different, I think, for each of these psychedelics, or perhaps different for every mental health indication. So that was one thing that I was thinking about.

(02:36:34):

And the other was that for dosing of psychedelics, I think as Mr. Barrow pointed out, one also needs to consider when it's appropriate to release a participant at the end of a dosing session and how much additional oversight they might need. And those considerations might affect the dose that you choose to use clinically. And I think he raised a very good point about anesthetics, and when we release people at the end of say, a surgical intervention. For psychedelics though, I also wonder if at the end of a dosing session, a participant might still be emotionally labile or experiencing a state of enhanced openness that might last beyond the acute effects of the psychedelic. And if so, should we consider that when we determine when to release them? So thank you. Those were my initial thoughts.

Susan Winckler (02:37:21):

Really helpful in helping us put some of that as in context and say, how should we be thinking about this, particularly the component about dose, not just thinking about the active ingredient, but the dose of other components with it. So I don't see Dr. Hendricks or Solage immediately unmuting, unless either of you want to offer a note.

Dr. Peter Hendricks (02:37:43):

I-

Dr. Martine Solage (02:37:44):

Oh, go ahead, Dr. Hendrick.

Dr. Peter Hendricks (02:37:46):

Okay, thank you. So a couple of things that come to mind for me. There are really two. One is, with regard to psychedelics, there is this notion that difficult experiences could in fact be therapeutic, and people sometimes respond that they've experienced a catharsis or emotional breakthrough. And so I do think we have to consider how we conceptualize difficult experiences, whether it makes sense to think of them as adverse events always, or whether there's actually in fact a therapeutic component to some very difficult experiences. I think psychedelics are unique in that regard.

(02:38:20):

I also think with MDMA looking like it could be available in clinical practice soon, there are questions around how MDMA, and this will be a question for psilocybin too, might be used in clinical practice. So the trials that were presented are of course efficacy studies, and they're wonderful. But I think a clinician might ask, well, what do I do if my patient does not respond to the first dose, or they do respond really nicely to first dose, but after some period of time experiences some remission of symptoms, what do I do then? There are questions I think around dosing parameters in a real world setting that will need to be answered in the future.

Susan Winckler (02:38:58):

Really helpful, Dr. Solage.

Dr. Martine Solage (02:39:01):

Sure. I just wanted to touch on some of the ideas that sort of stood out to me from a regulatory standpoint that I heard that the speakers bring forward. I appreciated that even though there's a lot of human experience with psychedelics that some of the experience that has happened outside of clinical trials, there's just a lot of uncertainty around the purity, around the dosing. And so just the need to collect data in a systematic way and that there's a lot to be learned from exploring dose.

(02:39:36):

And so I really in particular appreciated the idea that we have to sort of stick with, at least as a starting point, our usual approaches, our standard approaches to drug development, so that we're kind of being comprehensive and really thinking through all of the issues, which I think as Dr. Mitchell pointed out, maybe indication specific, patient population specific. And then I also just wanted to acknowledge some of the questions I think that Mr. Barrow raised and I come up in the discussion. I think also we'll be touched upon in some of our other sessions tomorrow in terms of set and setting and also sort of where FDA regulatory authority might lie and how it might intersect with other stakeholders in the system.

Susan Winckler (02:40:19):

Absolutely. Thank you, Dr. Solage. I was struck that we will get to some of these concepts later, and some are also outside the bounds of what we can possibly cover in two days. But let me then turn to a specific question and I'll turn, Dr. Hendricks, to you. So reflecting on what you heard and then other information, what do you think researchers should consider when determining a psychedelic dose? What are some of the components there? Oh, and you're muted.

Dr. Peter Hendricks (02:40:56):

Sorry, all this time on Zoom and I still haven't learned. I think that's a great question. And I will say first I think in these presentations, I think we learned quite a bit about how we might determine the optimal dose. I mean, obviously there's going to be, especially for newer, novel, or next generation psychedelics, a fair amount of preclinical work that will need to be done to establish important data around pharmacodynamics and pharmacokinetics and toxicology and so on. But when we get to the point where we're administering these drugs in humans, obviously one of our main questions is therapeutic response. Of course, we have to consider what a meaningful therapeutic response might be, and when we assess that outcome, that's something that I think is quite important. Again, I would turn to also the sort of challenging experiences that people can have on psychedelics and that we consider these aren't always adverse events, and sometimes in fact, they might be beneficial.

(02:41:56):

And in fact, we might see that, in some cases, participants appear to be doing worse before they get better. And this is not an uncommon outcome, as bearer probably knows with PTSD, and we know this in, for instance, exposure paradigm that sometimes people report feeling worse before they, in fact, improve. So I do think we have to carefully consider the time course of the therapeutic response and note that certain outcomes that we might think of as adverse events could in fact represent a therapeutic process that would play out over time. So I think we also have to consider when specifically our primary outcomes will be assessed because psychedelics are unique in that we might find a longer

term process at play and, such that, early in the process they may not appear to be therapeutic, but later they might.

(02:42:44):

Beyond that, I think our presenters gave us some really good ideas. It seems like we want to go with what is likely that the smallest dose that's going to provide the response we'd like to see, because as we increase the dose, some of the adverse events become more common. So I would say that, and then I would again emphasize how important it will be to inform clinical practice where our clinicians will still have a number of questions around how to administer these drugs when people either respond really well at first, or perhaps don't respond very well at first, or respond for some period of time before returning to baseline. And those are the sort of studies that I would really like to see, especially when MDMA and psilocybin come to market.

Susan Winckler (02:43:29):

Really helpful. And I'll just note, should they navigate the regulatory requirements. But yes.

Dr. Peter Hendricks (02:43:34):

Sorry.

Susan Winckler (02:43:36):

That's all right. It's just always a caveat of the regulatory environment. So Dr. Mitchell, would you pick up on that and say a bit more about the kind of number of doses in the sessions and how to think about determining that?

Dr. Jennifer Mitchell (02:43:56):

Sure. I think I'll start by reiterating something that Dr. Hendricks said, which is that I think if you have the time and the money dose response curves are the way to go, and that a couple of the panelists have already given us great examples of how these are so useful. So with respect to MDMA, I know I've heard Dr. Yazar-Klosinski mentioned before that low doses are actually anxiogenic, so we would perhaps want to stay away from those clinically. And I heard Mr. Barrow mentioned the difference between the biggest subjective effects that he saw at one dose versus perhaps the biggest clinical effects he saw at another. So I imagine that the process that the panelists are currently embracing is definitely a good one to follow that way. And then I think it also depends a little on whether we're trying to dose over other medications.

(02:44:46):

So like SSRIs, for example, they're very prevalent within these clinical populations, I believe. And they rely on serotonergic activity. And so you could imagine that it's very hard to taper them out. And so the dosing for these drugs are going to, in some way, be dependent on the other drugs that the population are currently taking. And then I think I'd also mentioned that there are going to always be individual differences, I believe, with these drugs, and that was also touched upon with the psilocybin. And so it seems that we have still responders and non-responders for each of these medicines. There are still people that aren't being reached. And so the question is it just a question of dose or is it something else? And so I think that the take home point is that, even if we figure out a good average dose for each of these compounds and indications, it's likely not going to be a one-size-fits-all approach and we're going to need additional data to ascertain why some groups are different than others.

Susan Winckler (02:45:49):

So we'll continue to explore the effects and some of those components may relate to dose or just be a non-responder component. Excellent. Dr. Solage, so what research do you see as needed to better understand that dose-response relationship in the psychedelic studies?

Dr. Martine Solage (02:46:14):

Well, thank you. I think I really would just echo a lot of what has been said already about one, from a regulatory standpoint, we are interested in understanding the dose response with regards to efficacy and then how that might or might not intersect with the psychedelic effects, but then also looking at the dose response for safety. And then as we're saying, we're still in the phase of gathering data, but if any of these products were ever to get to the point where we're thinking about labeling and describing for practitioners what doses might be useful, if there is a dose that's been shown to be effective but potentially has some safety risk that might be associated with it and we don't have information to guide whether a lower dose could still be effective but potentially mitigate the risk, then that could be a regulatory challenge for us.

(02:47:15):

Then similarly, if the dose that's explored or that's evaluated in the study doesn't seem to have an effect, but we don't have information for us to understand whether perhaps a higher dose could be used including in different populations that might have differential responses. It's a regulatory challenge for us. So we certainly want as much information as we can to be able to help us with those decisions should those situations arise

Susan Winckler (02:47:44):

To help just illustrate who is the dynamics of the patients and the dynamics of the intervention. Yeah. Okay. I've got a couple of questions that I don't have tied to any of you, and so that means it's open season, and if you were to raise your hand and jump into them, I welcome that. So the first one, it relates to whether are there doses that are simply not scientifically justifiable that we should take off the table? Is that something that exists here? So I've got Rob and then Dr. Mitchell. Yep.

Robert Barrow (02:48:30):

Jen can go ahead if you want. I'm happy to wait.

Dr. Jennifer Mitchell (02:48:34):

You go.

Robert Barrow (02:48:35):

Okay. Well, I mean certainly it's compound dependent. If there were safety, when we look at, tie it in with a point that was made before as well, which is that when we talk about safety, I think it's very easy with this drug class to be somewhat categorical but not specific about what safety are we actually referring to. We think about things like emotional lability, right? I mean, if psychotherapy does that, people leave effective psychotherapy session and walk around and they're emotionally labile, and that's sort of normal course of life in some respects. So is that a safety risk? Is that something that we can mitigate? Is it something we should try to mitigate it? I think it's an interesting question. Doses that would be physiologically unsafe, certainly I think we could probably arrive at a conclusion if the clinical data supported it shouldn't be administered at that level.

(02:49:28):

Seemingly, I think across the class, particularly with the classic psychedelics and say on this call the psilocybin and LSD, there seems to be a substantial margin between where we see physiological risks and the kind of doses we're talking about. So we look at preclinical studies and even prior human, real world accidental or intentional illicit exposure or even prior research. I mean with LSD, there are studies where reported in the literature where patients were given upwards of 800 micrograms and the set and setting was that they were physically restrained to a bed. No one's advocating that we should be doing this. But I think that dose levels that are much higher than where we're seeing some real clinical activity in these early studies, there's a pretty wide lane there that we probably don't have a whole lot of concern about going slightly higher than the dose that have been tested and triggering some really troubling adverse event at this point.

Susan Winckler (02:50:28):

So certainly learning from what has been done, including all of the parameters of that. And then as was raised a couple of times, this definition of adverse event in the space may be somewhat what fluid, so I'll go to Dr. Mitchell and then Dr. Hendricks. Dr. Mitchell.

Dr. Jennifer Mitchell (02:50:48):

Well, Mr. Barrow talked about high doses, so I was actually going to talk about low doses. I think we talk a lot about microdosing, even though I don't think we have a lot of scientific justification at present for microdosing some of these compounds, or perhaps in the case of others, we don't think that microdosing is a good idea and yet microdosing keeps coming up. So I was just going to mention that as we start this conversation about justifiable doses.

Susan Winckler (02:51:12):

Do you want to add anything on microdosing? I was about to say I don't know that we've heard microdosing yet, and I was surprised. So now go ahead.

Dr. Jennifer Mitchell (02:51:20):

I mean, certainly there have been scientific studies that have attempted to demonstrate the efficacy of microdosing, and I don't personally know of any that has been sort of unequivocal at this point. It doesn't seem like there are great data for microdosing, and yet again, a lot of people I hear are doing this personally. They're engaging in a microdosing regimen, and yet there are no data to support that regimen. So I think that could be cause for concern.

Susan Winckler (02:51:43):

Yeah. Dr. Hendricks?

Dr. Peter Hendricks (02:51:47):

I wasn't sure if I was going to mention this beforehand, but it's been touched upon. So I think it's worth mentioning that for a long time now, it's been thought that there is unique synergy between the drug that's provided and the psychotherapy that's provided, right, such that they interact with one another. Now, we really don't have any data that might indicate precisely what that interaction might be or if there is indeed an interaction, but it has long been assumed, and I think in the first wave of research it was clear that those clinicians picked up on the fact that there is more to this than just a drug effect. So I

think when we are asking ourselves questions around dosing parameters, and a very important question that needs to be addressed is what sort of psychotherapy is provided? How much and by whom? And I would be surprised if we found that the psychotherapeutic component did not matter. In fact, I feel pretty confident that it does, but we don't have any data to inform that question just yet. And I think that's a priority.

Susan Winckler (02:52:45):

Yes. And I think ties to the idea that we should be thinking about dosing in that concept writ large of not only the actual product, but the therapy that might go with it. I'm going to go to Dr. Yazar-Klosinski first only because she hasn't had another chance at the mic. And then I'll turn to you, Mr. Barrow. Yes, Dr. Yazar-Klosinski.

Dr. Berra Yazar-Klosinski (02:53:08):

Thanks. So I just wanted to touch on how do we know that the therapies or the psychological intervention is an important component? And we feel that it is very important because we've actually standardized the therapy and we see a high degree of adherence to the treatment manual for MDMA-assisted therapy in both MDMA and placebo groups. And if you just look at the change in the placebo with therapy group, you can see that we're still seeing evidence of pretty good response to the therapy, although it is also conflated by factors such as participating in a clinical trial, which can make someone feel better, getting ready access to clinicians. However, in the case of PTSD, these are really chronically ill patients. They've had PTSD for 14 or 16 years on average depending on the study. And the fact that we can see that with the therapy and placebo arm, I think is notable and commendable.

Susan Winckler (02:54:18):

So Rob, I'm going to put you one behind Dr. Goodwin.

Dr. Berra Yazar-Klosinski (02:54:24):

Please do.

Susan Winckler (02:54:24):

Dr. Goodwin.

Dr. Guy Goodwin (02:54:25):

Well, just on the whole psychotherapy psychological support issue, I think you do have to distinguish between a treatment like MDMA and a treatment like high dose psilocybin because the experience is very different and the activity of the therapist is very different. And certainly our sense is that it's possible and our policy is now to really minimize what we do in the psychological support, really to concentrate on safety and preparation and to try and also concentrate on making sure that the therapist's behavior is consistent across the different phases. And I would just finally notice that the actual change in mood in TRD is so early that it actually takes place before integration can be done. And in fact, there's no evidence that the integration makes any difference. So it may be different for different conditions. It's certainly going to be different for different drugs. And so let's be sure that we know what we're talking about when we talk generally about the psychological support versus psychotherapy.

Susan Winckler (02:55:29):

Very helpful that we also want to be precise in our language in the description. Rob, go ahead.

Robert Barrow (02:55:35):

Yeah, I'll be brief. Just to say that the comment, one of the really intentionally in the phase 2 study we just reported results from, we actually eliminated any form of psychotherapy, any sessions before or after administration and did try to just isolate a pure drug effect. And that doesn't mean that providers or researchers aren't, when the patient comes in the door, they don't look away and not make eye contact. There's sort of normal interaction between individuals, of course, but that is nothing that rises beyond just how any clinical trial would be conducted.

(02:56:06):

And we saw, I think when we look across studies and it's very hard to do this, so of course there's limitations with what I'm about to say. The thing that seems to be apparent though is that the primary impact of heavy psychotherapy is to drive a nocebo response, that the more therapy is given, at least with the studies of classic psychedelics, the more psychotherapy or prep and integration, the more a reinforcement of expectancy bias, if one exists, is present.

(02:56:38):

And that seems to drive, again, across studies, huge caveat, more of an impact on the placebo response or the nocebo response than it does on actually imparting a clinical benefit to the magnitude of responders and quantitative response.

Dr. Peter Hendricks (02:56:54):

These are with your data, Rob, is that right?

Robert Barrow (02:56:57):

Yeah, I'd say these are apparent in our data, and I think again, as you look across other studies where there's a very clearly articulated heavy psychotherapy, I would call it, and some organizations have done, have really reinforced their view of psychotherapy alongside, again, I'm isolating these to psilocybin and LSD and these serotonergic agents. But in our data, we really eliminated any form of psychotherapy. We still saw these remarkable results.

Susan Winckler (02:57:30):

Okay.

Dr. Peter Hendricks (02:57:31):

That doesn't indicate that psychotherapy doesn't matter. It just indicates that there's a signal even when the psychotherapy is minimal.

Robert Barrow (02:57:38):

Yeah, I agree. And I would say that any mood or anxiolytic works better with psychotherapy. These are, SRIs work better when you add on psychotherapy as well, but they're not required to unlock a clinical treatment benefit.

Dr. Peter Hendricks (02:57:53):

Right. And probably worth mentioning that a drug would perhaps be more scalable if the psychotherapy required were minimal.

Robert Barrow (02:58:00):

Yeah, exactly.

Susan Winckler (02:58:03):

But important, I think that the component being it's an important part of dose to understand what else is accompanying the experimental product that's being used.

Dr. Peter Hendricks (02:58:18):

Yeah, and as Rob is saying too, there's probably a lot that we need to work on in terms of the expectations that are communicated to the participants. It sounds like if this is not done carefully, then you could end up with a disappointed participant, especially if they have very high expectations about what psychedelics might do.

Session 4: Durability of Treatment Response

Michael P. Bogenschutz, MD, Professor, Department of Psychiatry, NYU Langone Center for Psychedelic Medicine
Carla Canuso, MD, Vice President, Neuropsychiatry Clinical Development, Johnson & Johnson Innovative Medicine
Valentina Mantua, MD, PhD, Senior Staff Fellow, Division of Psychiatry, Office of Neuroscience, Office of New Drug, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
Charles L. Raison, MD, Mary Sue and Mike Shannon Chair for Healthy Minds, Children & Families, University of Wisconsin-Madison

Susan Winckler (02:58:36):

Yeah. Which tied very well into some things we heard in an earlier session, and with that then it tells me it's time to go to our next session. So thank you so much to each of our presenters and panelists for taking us through and illuminating some components of the topic of dosing. We appreciate that.

(02:58:59):

I will now invite you, you may leave the stage and I'm going to open up the virtual stage for our fourth session, where we want to speak to a component that came up here in session three related to durability of treatment response. We also heard about it earlier in the day, and to kick us off with our first presentation is Dr. Michael Bogenschutz, who is Professor in the Department of Psychiatry at NYU Langone Center for Psychedelic Medicine. Dr. Bogenschutz, if you would unmute and present your slides, that would be great.

Dr. Michael Bogenschutz (02:59:39):

Okay. Can you hear me?

Susan Winckler (02:59:40):

We can.

Dr. Michael Bogenschutz (02:59:41):

And I think I'm going to use the slides, operate your slides, so-

Susan Winckler (02:59:48):

Perfect. If you click on the screen-

Dr. Michael Bogenschutz (02:59:48):

... where do I find those?

Susan Winckler (02:59:49):

If you click, then you should be able to advance.

Dr. Michael Bogenschutz (02:59:55):

Okay. Okay. Like that. Okay, great. Thanks. Well thanks for this invitation, and it's a very stimulating topic and great line up of speakers. So it's an honor to be here. And I'm just going to talk in pretty broad terms about some of the main issues involved in thinking about durability of treatment response. And I'll use samples from the recent literature in psilocybin-assisted treatments and MDMA. So we'll go ahead.

(03:00:44):

So yeah, so I just want to define some of the main questions, summarize what we think we know, or at least maybe seeing based on recent studies, and then discuss a little bit more about what we might do to answer some of these questions.

(03:01:07):

So really the big questions in my mind are pretty straightforward, clinically-relevant questions. How can we maximize the durability of the effects within a treatment episode? And there's already been quite a bit of discussion about what an episode is and what the dose and the number of sessions and how far apart they are and so forth. So that's one question.

(03:01:33):

And then the other questions have to do with how we decide if and when to initiate a follow-up episode of treatment, either in the case of relapse or for relapse prevention or maintenance. So just thinking about it conceptually, there's really kind of a finite number of variables that the durability of effects could depend on and some of them we have control over. So there's obviously the drug and the dosage of the drug and the number of schedule of doses, and those are things that have been discussed pretty extensively in the previous presentations.

(03:02:19):

We can expect that the durability of effect may also depend on the indication, characteristics of study participants within those indications, whatever co-occurring treatment people might or might not be receiving, which could include psychotherapy, but also medications, certainly antidepressants and some of the anti-addictive medications are potentially compatible with psychedelic treatment. And then in terms of the effect, we just always want to be sure whether we're talking about the within or between group effects.

(03:03:03):

The between groups effects will, in general, over time there'll be more and more noise. Those effects will get smaller over time almost inevitably. But in terms of the treatment response, it's not inevitable

that the overall average symptom level will increase over time, but it may and so that's something that we need to investigate and deal with. So how do we decide whether and when to administer follow-up treatment? So a big factor of course is just the durability of effects in the primary treatment episode. If the symptoms never return, then the question maybe doesn't even come up. But if it does come up in a certain proportion of the population or pretty much all of the patients, then we're going to want to study the efficacy of follow-up treatment.

(03:04:05):

And really two ways of thinking about this. One is, that you want to intervene before the person has a exacerbation or relapse of their symptoms and maintain the effect. And the other is to wait and see and have a follow-up treatment be triggered by some form of increase in symptoms or risk or signal of that sort. And then of course, safety is also a major factor, which has to come into our thinking about whether to administer follow-up treatment.

(03:04:43):

If there's some kind of accumulative risk due to exposure to the medication, then we have to take that into consideration and what might be a very reasonable risk for a single episode with a long duration of action may become less acceptable as the number of treatment episodes increases and the risk accumulates. So on all three of these obviously will depend on not just the drug and the dose, but a number of patient variables that I talked about a moment ago.

(03:05:29):

So what do we know about durability of treatment episode effects then from the studies that have been done so far recently? And there's, while I think a lot of this isn't exactly definitive, I think there is a fair amount we can at least observe from the studies that have been done. So starting with the work with MDMA and PTSD, these are the main outcome figures from the two phase 3 studies. And this is a three-dose treatment episode combined with extensive psychotherapy, relatively high doses, total duration of treatment episodes about 16 weeks.

(03:06:17):

And what we see, at least as far as it's been followed, is that the magnitude of the treatment effect seems to increase over the course of the 16 weeks of treatment. And we can't say for certain whether that's effective cumulative drug exposure and/or psychotherapy or just a passage of time. But at least until that final follow-up point, which is at least six weeks after the final dose, the effect seemed to be maximal.

(03:06:52):

And we don't really know much quantitatively about longer term outcomes. And there is a six-month follow-up study that was attached to both of these studies, which we'll hope to see the results of before too long. But the hope is that these effects are long-lasting and will not diminish and perhaps even increase over time, but that somewhat remains to be seen.

(03:07:23):

So we'll want to see those longer term outcomes. In terms of longevity of effect, there just hasn't been any work done comparing different treatment paradigms in terms of the dose or the number of sessions or the psychotherapy. And those all could have significant effects obviously. We just don't have any information about treatment outside of this particular model. Would more treatment be a good idea for people who've responded partially or not? Is that a sign that it just isn't going to work? And again, we haven't had any re-challenge studies or anything of the sort.

(03:08:04):

So, and then safety issues with MDMA. I think we're largely pretty confident that the physiological risks and potential neurotoxicity are not a very significant concern and carefully screened patients receiving three doses like this, but over time, with accumulation of exposure, would that become something we need to worry more about? Don't know.

(03:08:32):

Okay. All right. So there's not enough time to talk about all the psilocybin programs, so I'm going to talk a little bit about the major depression studies, where we stand with that, and addiction treatment. So this is sort of the punchline slides from three recent randomized controlled trials and can see all three of them show nice separation between the high-dose psilocybin group, which is on the bottom, and the control condition, which is on the top.

(03:09:09):

And the doses here range from 15 to 25 milligrams in these particular two studies, three studies. And the duration of effect was at least three weeks out to six weeks. And again, we don't have longer term follow-up studies. Over the amount of follow-up that there was, you don't see a diminution of treatment effect for the most part except in the Goodwin et al study where they're still visibly separation, but the effect size decrease was no longer significant after three weeks.

(03:09:57):

So questions that obviously arise to my mind are, does the duration of response depend on the dose, number of sessions, the extent and content of the psychotherapy? Is one session enough for everyone or do a larger number of sessions, get a better response rate? And of course, we know very little about predictors of treatment response. Just looking at these studies, there's a question arises as to whether the treatment-resistant depression samples are going to be harder to treat and have smaller effects that would not be surprising. We know that treatment-resistant depression, that's what it is. And so it may be resistant to this form of treatment as well.

(03:10:53):

Oops, jumped ahead. Here we go. Yeah. Okay. Substance use disorders. So these are pictures from just studies that have been done with psilocybin in smoking cessation and studies that my group did with psilocybin for alcohol use disorder. And these addiction studies really, this is where the majority of the clinical trials were done in the 1950s and sixties with LSD and the treatment model then, and now for the most part has been high dose, no more than three sessions, combined with variable amounts of therapy, but a fair amount of preparation at the very least.

(03:11:41):

And here we do have more evidence of persistence of effect in the double-blind situation out to six months at least, and longer-term follow up suggesting that the gains are maintained longer than that. But in terms of the overall treatment effects, there's little evidence that it diminishes over that six month timeframe. So this is just, again, a couple of points in a large space of possibilities. So we have to wonder what about the substance that we're using, the dose, number of sessions, psychotherapy platform. In these multiple dosing regimes, there's a possibility of titrating the dose, which clinically seems to make a lot of sense. But we haven't compared that sort of strategy to other strategies. So again, we don't know. And what do you do with the people who don't respond and how do you know who's going to relapse?

(03:12:53):

So how do we look at these things? And I don't have time or really the expertise to talk about all the possible study designs, but just to start, even to start to address these issues, you immediately get into

considerably more complicated costly designs. So on the left here is just sort of the minimal design to compare one versus two sessions of therapy with say, high-dose psilocybin. And ideally, you'd want to have the two groups receiving the one session, the active session first or second to control for order effects.

(03:13:40):

So you're up to four groups right off the bat and you want to be able to measure effects after the first session, after the second session. So you've pretty much quadrupled your complexity of your study there just to answer this basic question. In terms of relapse prevention, this is where you're basically assigning people to an algorithm of treatment. And this is be an algorithm where you basically, if somebody has an adequate response, then they either get a booster session or they don't. And you could also do this with people who relapse rather than people who respond and answer a different question. But the point is, again, you have twice the groups, twice the sessions, probably at least twice the duration. And so the complexity immediately gets multiplied by about a factor of four. And these are really just the very simplest questions that you could start to ask. So, oh, what happened to my... That was out of order because I did want to say something about this. I thought that was going to be after that other slide, but talk a little bit about the elephant in the room of subjective effects, which was also talked about in the previous session.

(03:15:12):

So this is something that if we're trying to measure a drug effect, obviously we're just trying to control this and minimize the placebo effect. But as Peter said earlier, there's reason to think, if not believe, that there could be positive synergies and not just additive or less than additive interactions between the psychosocial treatment and the drugs.

(03:15:41):

So there's a lot of, at least half a dozen studies that have shown significant correlation between the subjective effects experienced by participants and the magnitude and duration of their response. And this doesn't necessarily mean that the subjective effects are the causal element, but that's one plausible explanation. And these effects may or may not be separable from whatever direct actions on the brain are also predictive of treatment outcomes.

(03:16:18):

So this is something that we need to measure, and we need to consider the possibility that the memories of these experiences actually do change the brain in a way that is not limited to the neuroplastic effects that we can think about in very reductionistic terms. So if that's true, we actually probably want to think about magnifying or maximizing that interaction and not eliminating it.

(03:16:51):

But again, the complexity that you get into immediately becomes pretty overwhelming. So it's very understandable that we've all tried to keep our study designs very simple, but these are all questions that are immensely clinically relevant and important. So I think we can't ignore them in the long run. So that's it. Yeah.

Susan Winckler (03:17:14):

Great. Thanks so much Dr. Bogenschutz, and certainly interesting overview and exploration of that component. I'm going to invite our next presenter up and then we will see you again, Dr. Bogenschutz for the panel discussion at the end of this session. But let's turn now to Dr. Carla Canuso from Johnson & Johnson Innovative Medicine, where she serves as Vice President and Head of the Neuropsychiatry

Clinical Development Department. And Dr. Canuso, we'll hear from you about something that is not a psychedelic per se, but can help us explore this topic. So, Dr. Canuso.

Dr. Carla Canuso (03:17:57):

Thank you so much, Susan. Can you hear me and see my slides?

Susan Winckler (03:18:02):

We can do both, yes.

Dr. Carla Canuso (03:18:03):

Awesome. Right, right, so as Susan said, I'm going to talk about esketamine nasal spray, which is not a psychedelic, but is a treatment that had novel mechanism of action, rapidly acting antidepressant with a novel mechanism of action, and more importantly for this program, had a novel paradigm of treatment that really needed to be established and characterized prior to approval.

(03:18:32):

And so I think many of the topics that you're talking about today, we grappled with. And so this can serve as a bit of perhaps a roadmap, I think provide some insights of how we dealt with some of these questions and really how we collaborated very closely with the FDA to think through all of the challenges and then develop a development plan that answered these important clinical questions to inform the use in clinical practice.

(03:19:09):

So here is an overview of the development program for treatment-resistant depression, that in totality, you can see that there were numerous studies, huge program, 19 phase 1 studies, four phase 2, seven phase 3 studies in treatment-resistant depression, and that's not to mention a whole other development program that we had going on as well. There were three short-term studies that are listed there, the transformed studies. Then there was one controlled maintenance of effect study, the SUSTAIN study.

(03:19:45):

There was an open-label safety study, and that was to ensure that we met our ICH numbers for safety exposures. And then at the time of approval, we had two other studies ongoing, a pivotal trial in China, another short-term study, as well as a continuation study or an open-label extension study that when patients completed the studies that are listed on that top row, they were able to roll into that study.

(03:20:17):

So two of the studies from this program served as pivotal: TRANSFORM-2, a short-term study, and SUSTAIN-1, the maintenance of effects study. So that was unusual in and of itself because up until this point in time, all of the oral antidepressants, at least those that were approved in sort of moderate times, completed the maintenance of effects study post-approval, and that the short-term studies were sufficient for the initial FDA approval and that the maintenance of effects studies were conducted as post-approval commitments.

(03:20:54):

And that really aligns with clinicians experience and adage that I was taught in my own training of what gets you well, keeps you well. But that wasn't really an adage that could be applied in the case of esketamine because we really didn't know how it’s going to be used in clinical practice.

(03:21:17):

So we had to establish the treatment paradigm. And some of the questions that are listed here, I think have been listed or have been touched on by other speakers in today's section, and apologies for some of those formatting errors. But we really needed to understand how frequently should a patient be dosed and how long should they be dosed initially? How long would a clinical response last if it was achieved with repeated dosing? And then could it be maintained? Could that response be maintained with an oral antidepressant, or were patients going to need to have booster doses of esketamine over time to maintain that responsiveness? And then if they need to boost their doses, what was the frequency of that and what was the dose of that?

(03:22:07):

And then finally, when you stopped a initial treatment of esketamine after achieving response or remission, would there be any sort of safety concerns in stopping? Would there be a just discontinuation [inaudible 03:22:24] syndrome? So many, many questions that we needed to really think about very early in the development program.

(03:22:33):

And FDA, as partners, gave very clear and consistent feedback throughout the development program, given how little was known when we started. And what was known was really based on a handful of single-dose studies with IV ketamine where we could see a rapid antidepressant benefit within hours. But we knew that that benefit was transient and that some sort of repeated dosing would be needed.

(03:23:07):

But like I said, the FDA was really very consistent in what they expected to see in the development program and questions that really needed to be answered through the generation of the data and the development program. So these are just a series of quotes that I've pulled from communications, I think from our pre-IND meeting through our end of phase 2 meeting.

(03:23:28):

So in order to approve product, we would need to be able to advise clinicians on how to best use the product after initial response. Due to its uniqueness, and this is safety concerns, questions about how to maintain response, we view esketamine very differently than previously approved oral treatments. We would therefore need to see maintenance data at the time of file.

(03:23:51):

They also said that given the great importance of the maintenance of effects data, that they would consider one positive short-term study along with one positive maintenance study to be sufficient for the NDA submission, so that the two adequate controlled clinical trials to achieve the evidentiary standard could be done with a short-term and a maintenance of effects study, which was also unusual.

(03:24:20):

But they also gave a caveat that the duration of the maintenance of effects study and the randomized withdrawal phase really needed to be sufficient, or the study would not be useful in yielding information regarding how patients could be maintained on oral antidepressants after they had been stabilized on esketamine.

(03:24:49):

So the first thing that we really wanted to establish, and this is actually data that was from our IND opening study, was what was the frequency of dosing in what we call the initial induction period? Like I

said, we knew that a single dose wasn't going to be sufficient and that there was going to be a transient effect and that there would be the requirement at least initially for more frequent dosing.

(03:25:18):

And so this study was done to establish what really would be the minimally-effective frequency, and we looked at twice a week versus three times a week, and we saw that they were equally efficacious in maintaining the effect over the short period of time. So that informed us to the dosing frequency of our short-term study, and we went with the less frequently twice-weekly dosing.

(03:25:46):

So then the next big question was the design of the short-term study. But really the design of the short-term study was very much influenced by the thinking of how would patients be treated after a short-term induction of esketamine, after patients were improved and made well on esketamine. Could they be maintained on antidepressant alone or would they need to have continued esketamine after this study?

(03:26:20):

So because of that key question in the overall treatment paradigm, we decided that we would run the short-term studies with esketamine added to a newly initiated oral antidepressant as one of the treatment arms. So esketamine plus a new oral antidepressant versus a new oral antidepressant plus an intranasal placebo. And patients were dosed twice-weekly with study medication and the studies were run for a period of four weeks. And then the four weeks also allowed for a reasonable comparison of esketamine plus the oral antidepressant versus the newly initiated oral antidepressant alone, which by four weeks, should at the very least begin to show some treatment response.

(03:27:16):

As I said, the short-term study was designed with the longer-term treatment paradigm in mind, and here is a schematic of the maintenance of effects study. And I know that this is a rather busy slide, so I will talk you through it, but patients who participated in the short-term TRANSFORM study, so these are the patients that were in the four-week induction period. Those who were responders were able to roll into the optimization phase for the maintenance of effects study.

(03:27:51):

We also had direct recruitment and patients coming through that channel received the open label esketamine for four weeks. And then patients were optimized. Those who were stable responders or stable remitters were then randomized to continue on the intranasal esketamine plus the antidepressant, or to have the esketamine withdrawn and to continue simply on the oral antidepressant. And one of the features that was really both unique and I think informative about this design is that we use some individual dosing frequency during the optimization and maintenance phase of the study.

(03:28:34):

So after the twice-weekly four-week period in the induction, in the optimization phase, in the first four weeks, patients dropped down to weekly dosing, and then, thereafter, based on their actual symptom severity, as measured by the [inaudible 03:28:51], they would either continue on weekly dosing or go to every other week dosing. So that then gave us very good information about whether or not patients needed to continue with booster doses and how frequently or infrequently patients could be maintained. And the data were positive. Esketamine was very significantly effective in reducing relapse, both in the remitters and the responders, both in patients receiving it weekly and every other weekly. And details of the dosing frequency are in the product labeling.

(03:29:37):

We also had that open-label continuation study that I mentioned, and this study was done initially for the long-term safety and tolerability and to allow access to the drug to patients prior to approval. But the FDA also asked us at the time of approval to continue to collect data in that study, primarily to characterize the effects on cognitive function and urinary symptoms. That study went on for three years plus. And I'm just showing the maintenance, I mean, I'm showing the efficacy data, even though this was primarily a safety study, but this is data where I think the mean exposure was close to four years in subjects. And you can see from these data on the [inaudible 03:30:26] that the efficacy was maintained over the long period of time in the patient population, which started out over a thousand at the time that it started, and then over time fewer patients, but quite a large and long study.

(03:30:47):

To summarize, what were the key takeaways and learnings from this experience that I believe are applicable to the field of psychedelic drug development is really consider how is the treatment going to be used in clinical practice and generate the data to support this? And really as a clinician, what would you want to know about this product? Treatments with novel mechanism of actions and new dosing power lines are going to really require unique and customized clinical development plans to inform labeling and clinical use. Durability of effect I think becomes even a greater factor in the overall benefit-risk assessment of a novel therapeutic when there are some safety and abuse liability concerns.

(03:31:35):

And then depending on how a treatment's going to be used in practice, maintenance will affect studies, it may very likely be required pre-approval. But the post-approval data collection can also further inform durability of effect, as you saw in that long-term study. But most importantly, collaborate with the regulators early and often. We did and they were really great thought partners through the entire process. I'll stop there.

Susan Winckler (03:32:04):

Dr. Canuso, we really appreciate you sharing the experience and the dynamics of all it is that you navigated there and it gives us a lot to think about and discuss as we come into the panelist presentation, so thank you. And if you would stay on camera, I'll invite Dr. Bogenschutz to return to the camera and introduce the two new faces that we have for our discussion. First new face is Dr. Valentina Mantua, who is Senior Staff Fellow in the Division of Psychiatry at FDA's Center for Drug Evaluation and Research, and the focus of her work is on psychopharmacology, drug development, regulatory agencies, and digital health technologies.

(03:32:48):

And our second new face is Dr. Charles Raison, the Mary Sue and Mike Shannon Chair for Healthy Minds Children and Families at the University of Wisconsin-Madison. In his most recent work, Dr. Raison has taken on a leadership role in the development of psychedelic medicines as potential treatments for major depression. Let me open as we have with our other sessions, and I'll first say to Dr. Mantua and Dr. Raison, do either of you have any questions for Dr. Bogenschutz or Dr. Canuso as we jump into this session? Any questions or something that struck you that you want to highlight? Go ahead, Dr. Mantua. Yep.

Dr. Valentina Mantua (03:33:33):

Yeah, perhaps not really a question, but maybe a point of clarification because both speakers have touched upon this issue, which is a slight, however, important distinction between durability of response

and actual maintenance of effect. It is really only semantic, but it is important because they ask different clinical questions, right? Durability of responses in a short term within the index episode, whatever disorder you want to consider, whether this is depression, which is episodic, it's PTSD, et cetera. And maintenance of effect is when should we do re-treatment? What happens next? What if the recurrence comes and what happens in the long term if one has benefited from the drug but symptoms come back? Can we re-dose? These are two slightly different concepts from both a clinical perspective and a regulatory perspective.

Susan Winckler (03:34:33):

Thanks for that distinction. Dr. Raison?

Dr. Charles Raison (03:34:35):

Yeah, I just want to make a comment. I'm so struck by the need to show long-term durability for FDA approval. We should highlight this is new, right? Dr. Canuso made the comment, the dose that gets you well keep you well, and certainly that was what I was raised on, but we know now that a fair number of people that have initial response to a standard antidepressant will lose it. You know that tachyphylaxis rates, some studies up to almost 50%, more than that in STAR*D. This idea of course was if you're taking the medicine at six weeks, you're going to be taking it at six months. And if it worked at six weeks, it worked at six months, which is only partially true.

(03:35:13):

I think one of the things we should honor here is that this is a brand-new kind of day where you have some kind of treatment that's in the body for a few hours and then produces these self-sustaining, long-term effects. There's a punishment there, and I understand there's probably no escape from it, but as Dr. Canuso was saying, all of a sudden now there's a new layer that's added on to the challenges of FDA approval. How long does it last? And nobody ever had to do that before. We should have a little pity party for psychedelics.

Susan Winckler (03:35:48):

Or at least the discussion to say how to navigate in a novel environment. Yeah, yeah. That's helpful. Let me stay with you, Dr. Raison. We heard a bit about this, but what would you articulate as the factors that impact this durability of treatment effect? What would you want to say about that?

Dr. Charles Raison (03:36:09):

Well, I've been listening to the whole entire thing today, and two things that have come up repeatedly are blinding and durability, and they seem not immediately connected, but I think they are because I think at the end of the day, everything comes down to the question of whether the conscious experience, and if you want to be a reductionist, the brain activity that subserves it, is required to induce these long-term effects. We don't know. But of course that's a problem with blinding because it's very hard to blind that. And it's also a question around durability because the evidence that, and certainly in healthy volunteers, even back to Roland Griffith's time, that the intensity of certain aspects of the psychedelic experience seems to predict these long-term outcomes.

(03:36:52):

In my academic work that we do at UW, what we're interested in is two things. One, can we separate consciousness from the underlying biology? That turns out to be not so easy, but we're trying. And the second thing is, what if we just give up? This isn't for FDA approval, but I'm trying to understand how to

optimize these agents. What if we gave up on blinding? We do studies now where we give everybody psilocybin and we look, can we extend the durability of the effect by adding something to it afterwards? You do away with this question. Everybody gets that same, we could argue all day about why the psilocybin is doing it, but punt that down the road and say, "Okay, if we take it as a given, it seems to be doing something of great value. Can we extend it?" So, that.

(03:37:40):

And then the other thing I would say is yeah, I mean, Dr. Bogenschutz laid it all out very nicely. I am struck, and I can't prove it to you, but one of the interpretations of the data I think that exist right now is that psychedelics and MDMA may work better for conditions that are characterized by people struggling with a definable problem. If you look at the durability of response, perhaps the depth of response, you see these large scale responses saying people that were previously high functioning that have cancer, four and a half years later, many of these people are still in remission. Steve Ross's data from NYU. You see these very long-term responses to MDMA and people that are dealing with PTSD, which of course is an octopus like syndrome, but people are often struggling with a particular thing. And then in Dr. Bogenschutz's study, people struggling with an alcohol abuse disorder are also struggling with a certain thing.

(03:38:39):

And especially when we think about addiction, there's a long history of people having these quantum change phenomenon where people will stop drinking, the AA phenomenon. And I've often thought that psychedelics mirror that in some way. People have these experiences, and then afterwards, just setting aside all the complexity we've talked about, some subset of people just change and they change for an extended period. Although depression and treatment-resistant depression are huge targets, and I think these agents are going to be valuable, the question of durability is going to maybe be more challenging because when people have been depressed for years and years, the odds of getting one of those quantum changes that a one and done, I think become much, much smaller. Looking at everything we've been talking about, but especially the possibility that certain indications might be more tailored made for these long-term durable responses is something at least that I'm very fascinated by.

Susan Winckler (03:39:36):

Mm-hmm. Mm-hmm. That perhaps not surprisingly, but thinking through the indication and the durability and what is it that we're exploring there and where those indications... Just we may have more to learn there.

Dr. Charles Raison (03:39:51):

Yeah, and there's some interesting challenges. End of life is not something yet that the FDA has been able to put a indication around, and yet man, many of us in the field think that that is just such a prime target. It's an example of how the targets that might be especially responsive may not in any simple way fit into the box that produces approval.

Susan Winckler (03:40:10):

Mm-hmm. Mm-hmm. Let me turn then, Dr. Mantua, to you and ask a little bit more, your insights as we think about all of this research that's being done, what research is needed to further determine how often psychedelics should be administered? I think you distinguished... Oh, and I lost you there. I want to make sure, Dr. Mantua, you're still with us.

Dr. Charles Raison (03:40:43):

It's always the technology, isn't it?

Susan Winckler (03:40:54):

Yep, it's always the technology. Well, then she can't answer my question.

Dr. Charles Raison (03:40:59):

Should we keep chatting then?

Susan Winckler (03:41:01):

We will. We absolutely will. And this may be to you, Dr. Canuso, but I'd welcome all of you to chime in. What do we know about long-term safety of repeat dosing?

Dr. Carla Canuso (03:41:25):

Directed from me, I mean, the study that I showed for esketamine was that there was no new safety signals that were observed in the long-term study compared to what we knew at the time of approval. The additional three years did not yield any new insights around safety, other than it was safe, that there are not major new safety concerns. No.

Susan Winckler (03:41:49):

Right. [inaudible 03:41:52] Yeah. We can ground in that both looking and then the results from that. Dr. Bogenschutz and Raison, what do we know in the psychedelic space specifically?

Dr. Michael Bogenschutz (03:42:07):

From the clinical trials, I think we know nothing because we've never given somebody one of these drugs more than two or three times. I mean, from natural history, I mean, we know there are millions of people who have taken these, many of these drugs, many, many, many times and we worry about valvulopathy or other serotonergic things that can happen, and there's no evidence that those things are more prevalent in those people who've used psilocybin a bunch of times. But it hasn't been necessarily, those aren't experimental studies, so it's nothing that FDA is going to consider as definitive of course. But I mean, it does tell you something about overall toxicity and rates of adverse events in uncontrolled situations, which those rates will probably be higher in general from rates in less controlled, in more controlled situations, so it sets an upper bound on how dangerous we think these drugs might be if we use them in a carefully controlled way over time. But those are very soft data compared to what we collect in trials, so those studies just haven't been done.

Susan Winckler (03:43:29):

Mm- hmm. Mm-hmm. And helpful, thanks Dr. Canuso, for grounding us in what we know about yours and how you did it, and then the piece that we simply don't have more than soft data. Dr. Mantua, welcome back. Sorry about that. As we all know, technical dynamics emerge. I was going to turn to you for a question to say, what would you articulate as the research needed to determine how often psychedelics should be administered?

Dr. Valentina Mantua (03:44:05):

Well, as I said, it really depends on what is the question that a clinical trial, therefore, an experiments intended to answer. If we are in an acute phase of depression, for example, or we're seeing a patient

that is not responding or we're seeing a patient with PTSD, there is a minimal observation period that we need to understand whether psychedelics work in the context of the index episode. Let's say that it would be six weeks, nothing is written in stone, but approximately six weeks for depression and I don't know, 12 weeks at minimum for PTSD, and any depends on the indication. Within that period of time, we need to gather information at phase 2 and from other clinical data that are out there to inform if one dose or two dose or three doses are needed. And what is the distance between these?

(03:45:01):

Now, for the most part, we don't know. And I think that the role of the regulators, it was clear from Dr. Canuso's presentation, instead of working together with developers and try to build this experiment together in a way that it does answer the clinical question. I guess everything becomes a lot more challenging when one goes beyond the index episode into recurrences. If there are, if there's a chronic disorder, if symptoms come back, there we really have very little information as for now and very hard challenges.

(03:45:35):

One of above every one else is randomization. If patients have been in a double-blind phase during the first treatment of the index episode and then get re-randomized into different treatment, they would understand what they're on. And so that is an additional problem. Another additional problem is what would be the lifetime use of the drug? Would it be a booster once a year? Would it be three times a year and for how many years, right? That changes all our safety requirements, both from a non-clinical and a clinical perspective, as you've heard, esketamine was applying the ICH E1A requirement for exposure, so that this would apply for chronic exposure. I think these are in a nutshell all the challenges that we face when we try to answer these two main clinical questions on the drug use.

Susan Winckler (03:46:41):

Mm-hmm. And so, distinctly need to be thinking more and then thinking about longer term follow-up and assessment. I might just open this to all. How would you think about re-dosing if the durability of responses is not maintained for very long? Dr. Raison, do you want to pick that up? And then Dr. Bogenschutz, I might tag you to follow on.

Dr. Charles Raison (03:47:15):

Sure. Well, when I put on my [inaudible 03:47:16] hat, this is obviously, as Dr. Davis was saying earlier, this is a huge question because how do you think about it? In a perfect world, you'd randomize people to get the active or not, and then you just follow them for however long you want to follow them. That's very difficult to do and there are almost no standard antidepressant studies that have done that. Usually what happens is they do some sort of withdrawal in the responders or something like that. And so asking people with desperate depression who may have gotten a placebo in the initial phase of a study like this to just keep hanging out is probably unethical and intractable.

(03:47:54):

One challenge you have, then of course, is that when you look at people who haven't responded to initial treatment, especially if you're still blinded, you offer everybody the psilocybin. Of course, now it's a different kettle of fish because you've got an open trial. That's going to affect, we know that the presence of placebo reduces responses in general, so that's going to impact things. And then you have to ask yourself, well, do we re-dose when people start relapsing? Is that what we should do? You really want to be giving people a psychedelic whether they need it or not? Or do you give it to them whether they need it or not? We don't know that either. And then how long do have to follow up for? And these

are really, really complex questions, but of course they have to be done and there's going to be some kind of compromise here, but those are some of the big issues I think.

Susan Winckler (03:48:41):

Mm-hmm. Yeah. Dr. Bogenschutz?

Dr. Michael Bogenschutz (03:48:46):

Yeah, I mean, I agree with all of that and getting people to actually do these studies even if we felt we had the right design over years and in spite of whether they're relapsing or not. But I think it's potentially a good place for open-label designs where you just, let's say people respond initially and they say, "Well, we're going to randomly assign you to an algorithm of treatment and you're going to get another episode of treatment every six months whether you need it or not, and you're not except for need, and you're never going to get it again, sorry," for example. And then you're going to have a huge amount of attrition from those studies over years, but at least you're comparing apples and apples at that point.

(03:49:40):

I think the other thing, just to follow up on what Chuck said earlier, was about how do we think about... Can we think about these as, is it reasonable to think about these treatments as curative? And it really depends on how we think about the illnesses and ultimately it becomes a little bit tautological or circular because we might think recurrent major depression, it's a trait, it's just the way you are after you've had it for a certain amount. That's a chronic illness as we classically think about it, and you're probably going to need ongoing treatment, but until we find something that cures it and then that's different. I mean, you can't really count on that reasoning.

(03:50:25):

Addiction is, I mean, we talk about it as a chronic illness, it often is, but it's in principle, curable. I mean, because the behavior can stop and the brain can recover a lot. And PTSD also, it's not so much a relapsing disorder unless somebody has another episode of trauma. If it goes away, we don't expect PTSD to come back. Addiction might come back. Depression, we think it will come back, but that could change. And end-of-life anxiety, it will go away eventually because-

Dr. Charles Raison (03:50:58):

You'll die.

Dr. Michael Bogenschutz (03:51:00):

... the end will come. But beyond that, yeah, I don't know.

Susan Winckler (03:51:03):

Mm-hmm. Mm-hmm. Which is an interesting lens of the flip side to Dr. Raison's observation about where these products might be most helpful, and I think that lens of curative is another way to think through that. We have just a few minutes left and so I want to open it up. Is there anything else that you'd like to observe just as we think through the questions here and the components as it relates to durability of treatment response? I know, Dr. Canuso, anything else you want to add from the esketamine experience? And obviously as we know, anytime a product is approved, there's perpetual monitoring separate from specific trials, but every product that's approved has, in perpetuity,

monitoring for adverse events and just it's a reality of having reached that status. Anything else you want to share?

Dr. Carla Canuso (03:52:19):

Well, just two comments that are somewhat unrelated, but Dr. [inaudible 03:52:24] talked about work in phase two that also informs the durability of the short-term treatment, and we did do other studies where we were informed about which dose might give us the longest durability in between dosing intervals. We selected the doses that we thought would give that longest durability. That was point one.

(03:52:48):

And then point two is obviously, with the treatments like esketamine and psychedelics and having very structured safety monitoring, and in the case of esketamine, a REMS is very, very important so that you continue to collect data because even our clinical trials, and as big as our program was, I think it was over whatever [inaudible 03:53:11], 1700 patients, it's small relative to the general exposure, and infrequent events may not be captured even in a development program. And so it takes a long time to fully appreciate the safety profile of a drug, and especially if it's a drug that's not going to be used frequently or chronically, and it may be sometime before it declares itself.

Susan Winckler (03:53:37):

Right, right. You have the dynamics not only as, as often said, clinical trials are not real life, and then just further unique dynamics here of a perhaps discrete use versus continued depending on the intervention. Okay. Dr. Mantua, did you want to chime in? Anything else you want to add on the topic?

Dr. Valentina Mantua (03:54:04):

Well, yes, another big question mark that we have is, are psychedelics given in isolation or not? Because so far we do not have sufficient information as to what is the drug interaction, what is the interaction with currently available therapies? We've been scared for some time, now we're seeing more bold tentatives, and I guess this is an important information because if there's something in the background, either psychotherapy or another treatment, that would change the length of time a patient can be off treatment. And also, I was hearing Guy Gutwin this morning, in his phase 2 study, the longest period of time that they could take patients off treatment before clinicians wouldn't think about giving another one was three weeks with a single dose psilocybin. I didn't have that information about that trial. And so this is something to think about. What else do you give psychedelics with?

Susan Winckler (03:55:08):

Mm-hmm. Mm-hmm. And capturing that information and then better understanding that dynamic. All right, any last words from this?

Dr. Charles Raison (03:55:20):

Just real quick. I heard Dr. Facciani mentioned that real world things are going to be looked at. Legalization is moving very rapidly. Places like Colorado, these things are going to probably be able to be prescribed by doctors for conditions and working with states to see if we can get a sense of what happens there would be potentially a data source in the thousands and thousands.

Adjourn

Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler (03:55:43):

Mm-hmm. Mm-hmm. And a different type in that it's the real world data to then yield real world evidence, but it's still information. And actually, we'll touch on that in our final panel tomorrow. With that, I am going to say thank you so much to each of you for joining us today for this panel to close out our discussion for day one in exploring questions related to durability of treatment response.

(03:56:12):

Just a quick reminder that we will convene again tomorrow. We welcome each of you to return and a special thanks to our speakers and panelists from today and those who we will see tomorrow. We resume at 10:00 AM Eastern time with three more sessions where we'll talk about set and setting and overview of FDA regulatory authority, and as we just talked about, considerations for potential use of psychedelics in the real world and what we can learn from some of the existing real world data. Finally, we will be posting the recording and other materials for this event on the foundation website, ReaganUdall.org, by next week. Thank you so much and we hope to see you again tomorrow.