FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS

ADVISORY COMMITTEE MEETING (PDAC)

Friday, July 18, 2025

9:00 a.m. to 3:54 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. NARENDRAN: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. All members of the public are reminded to silence their phones and other devices, and to otherwise refrain from disrupting the meeting. Loud talking or applause may make it difficult for meeting participants and observers to hear the proceedings.

My name is Raj Narendran, and I'll be chairing this meeting. I will now call the July 18, 2025 meeting of the Psychopharmacologic Drug Advisory Committee to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We will start with the FDA to my left and go around the table.

DR. BURACCHIO: Teresa Buracchio, Director of the Office of Neuroscience in CDER at FDA.

DR. FARCHIONE: Tiffany Farchione, Director

of the Division of Psychiatry, also in CDER at FDA.

DR. MANTUA: Valentina Mantua, Associate Director, Office of Neuroscience, CDER, FDA.

DR. FISCHER: Bernie Fischer, Deputy Director, Division of Psychiatry, CDER, FDA.

DR. YANG: Peiling Yang, Supervisory Mathematical Statistician, Office of Biostatistics, FDA.

DR. NARENDRAN: Dr. Thomas, if you want to introduce yourself online?

DR. THOMAS: Patrick Thomas, Baylor College of Medicine.

DR. FIEDOROWICZ: Jess Fiedorowicz, University of Ottawa, with adjunct appointment at University of Iowa.

DR. NARENDRAN: Dr. Raskind?

DR. RASKIND: Hi. I'm Murray Raskind. I'm a psychiatrist at VA Puget Sound in Seattle and the University of Washington.

DR. NARENDRAN: Dr. Shaw?

DR. SHAW: Hello. I'm Pamela Shaw. I'm Senior Investigator of Biostatistics at Kaiser

Permanente Washington Health Research Institute in Seattle, Washington.

DR. DUNN: Walter Dunn, Assistant Clinical Professor, University of California, Los Angeles.

DR. NARENDRAN: Raj Narendran, psychiatrist, University of Pittsburgh and UPMC Health System.

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

DR. BLOCK: Laura Block, patient advocate.

DR. BALLON: Jacob Ballon, Associate Professor of Psychiatry, Stanford University.

DR. SHINER: Brian Shiner, Associate Chief of Staff for Research at the VA Vermont Healthcare System and Associate Professor of Psychiatry at Dartmouth.

DR. SIMON: Greg Simon, psychiatrist at the Washington Permanente Medical Group and investigator at the Kaiser Permanente Washington Health Research Institute.

DR. COFFEY: Chris Coffey, Professor of Biostatistics, University of Iowa.

DR. CANUSO: Carla Canuso,

Johnson & Johnson, industry representative, non-voting member.

DR. NARENDRAN: Thank you.

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

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

conclusion. Also, the committee is reminded, please refrain from discussing the meeting topic during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. FRIMPONG: Thank you, Narendran.

The FDA is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the Federal Advisory Committee Act of 1972. At today's meeting, the committee will discuss supplemental new drug application 205422/S-012, for Rexulti, brexpiprazole, tablets, submitted by Otsuka Pharmaceutical Company, Limited, for the proposed indication of treatment of adults with post-traumatic stress disorder, in combination with sertraline.

With the exception of the industry representative, the members of the committee are either special or regular government employees and are subject to federal conflict of interest laws and regulations. Accordingly, FDA has reviewed the

financial interests of the committee members for compliance with federal ethics and conflict of interest laws. We have screened the members for potential financial conflicts of interest related to today's meeting agenda, both their own interests and those that are imputed to them, including those of their spouses, minor children, and employers.

Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers under 18 U.S.C. 208 have been issued in connection with this meeting.

Dr. Carla Canuso of Janssen Pharmaceutical Companies of Johnson & Johnson is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Consistent with Commissioner Makary's April 17, 2025 statement, FDA is only including industry representatives in advisory committee meetings where required by statute. FDA is required to include an industry representative in today's meeting under 21 U.S.C. 355.

Industry representatives are not appointed as special government employees nor are they regular government employees. Industry representatives serve as non-voting members of the committee. Non-voting industry representatives represent all regulated industry and not any particular association, company, product, or ingredient, and bring general industry perspective to the committee.

Under FDA regulations, although a non-voting member serves in a representative capacity, the non-voting member shall exercise restraint in performing such functions and may not engage in unseemly advocacy or attempt to exert undue influence over the other members of the committee.

We would like to remind all members of the committee that if the discussions involve any other products or firms not already on the agenda for which you have a personal or imputed financial interest, you must recuse yourself from that discussion, and your recusal will be noted for the record.

FDA asks that all other participants, including the industry representative and open public hearing speakers, advise the committee of any financial relationships that they have with any affected firms, its products, and if known, its direct competitors. We would like to remind the members that if the discussions involve any products or firm not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. Thank you.

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

FDA Opening Remarks - Tiffany Farchione

DR. FARCHIONE: Hi. Good morning, everyone, and welcome to this meeting of the Psychopharmacologic Drugs Advisory Committee. Today we're going to discuss Otsuka Pharmaceuticals' application for brexpiprazole to

be used in combination with sertraline for the treatment of post-traumatic stress disorder or PTSD. This is a somewhat unusual program, so I want to take the time to give you just a brief introduction to the issues we'll be discussing today.

As you know, PTSD is a severe and disabling psychiatric condition that can develop after exposure to actual or threatened death, serious injury, or sexual violence. It's characterized by intrusive memories, hyperarousal, and avoidant behavior. Comorbidities are common, and PTSD is associated with a high risk for suicidal ideation and behavior. Patients with PTSD experience impairments in social and occupational functioning and diminished quality of life.

There are currently just two medications approved to treat PTSD, both of which are selective serotonin reuptake inhibitors. One of these, sertraline, is a component of the proposed treatment paradigm under consideration today. Of note, response rates for individuals with PTSD

treated with SSRIs rarely exceeds 60 percent, and even fewer patients achieve full remission. Thus, there remains a significant unmet need for additional safe and effective treatments.

Nonetheless, paroxetine and sertraline are considered standard of care pharmacotherapies for PTSD. In fact, when it comes to pharmacotherapy, existing clinical practice guidelines recommend monotherapy. For example, the most recent Veterans Administration and Department of Defense clinical practice guideline cites a lack of data to support use of other medications, including atypical antipsychotics, together with recommended pharmacotherapies, though the guidelines stop short of recommending either for or against the practice.

The application under review attempts to address the lack of data, with studies evaluating the use of brexpiprazole and sertraline initiated at the same time for the treatment of PTSD. This paradigm is novel. Typically in psychiatry, a prescriber would initiate one treatment at a time, waiting to evaluate a patient's response to that

treatment before making changes or adding a second medication. That is not the model under review today. The applicant is not seeking an adjunctive indication, and we have no data examining the addition of brexpiprazole to an SSRI in the context of inadequate response. The committee is only being asked to consider the data in support of co-initiation.

So although this paradigm is unusual, the agency did not object to the applicant's program. We did, however, outline some expectations as to the evidence needed to support the proposed co-initiation paradigm. At the end of phase 2 meeting, we let the applicant know that for their phase 3 studies, they could consider eliminating the placebo arm.

Given that sertraline is already approved for the treatment of PTSD on its own, the relevant question here is whether the brexpiprazole plus sertraline combination is superior to sertraline alone; in other words, does adding brexpiprazole to an approved treatment confer additional benefit

beyond what would be achieved with the approved treatment alone?

We also advised the applicant that they would need to provide substantial evidence of superiority to sertraline alone. The applicant designed their phase 3 program to do just that. They conducted two large adequate and well-controlled studies comparing brexpiprazole plus sertraline to sertraline plus placebo. One of those studies was robustly positive; the other was clearly and convincingly negative.

Despite extensive exploratory analyses, we have been unable to identify a reason for these discordant results. Thus, we cannot rely on the phase 3 studies alone to provide substantial evidence; so the applicant has asked us to consider the data from their phase 2 study. You'll hear the details of this study later this morning, but it's similar to phase 3 studies in many respects. However, it was designed to be an exploratory study to generate hypotheses and inform the design of the phase 3 studies, and because the hypotheses were

selected retrospectively and multiple testing procedures were applied post hoc, statistical significance cannot be claimed for those study results.

So although the main question for consideration today is whether efficacy has been demonstrated for brexpiprazole plus sertraline, I do want to take a moment to discuss safety. The adverse events reported during the clinical trials were consistent with the known effects of both drugs. So although no new safety signals were identified, subjects experienced events consistent with the known risks of brexpiprazole and the known risks of sertraline. We will need to consider the evidence of benefit in the context of those risks.

So today, we have three questions for discussion and one voting question for the committee. For the first discussion question, we're going to ask the committee to discuss the strength of evidence provided by the two phase 3 studies, Study 00071 and 00072, and in particular to discuss the impact of the discordant results on

your overall assessment of efficacy.

We'll also ask you to discuss your view on the contribution of Study 00061 to the overall evidence of effectiveness. Then, based on the available data, and with consideration of the known risks of brexpiprazole and sertraline individually, we'll ask you to discuss the acceptability of the proposed concurrent initiation treatment paradigm.

And finally, we'll ask you guys to vote, and the question for voting is, based on the available data presented, has the efficacy of brexpiprazole, when initiated concurrently with sertraline, been established for the treatment of PTSD? And we'll ask you to provide your rationale and indicate any specific information like the statistical analyses or other data on which you based your vote.

And with that, I will pass it back over to Joyce. Thank you.

DR. NARENDRAN: Thank you, Dr. Farchione.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at

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

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

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

We will now proceed with the presentations from Otsuka Pharmaceutical Company.

Applicant Presentation - Mary Hobart

DR. HOBART: Good morning. I'm Mary Hobart,

Senior Vice President of Global Regulatory Affairs at Otsuka Pharmaceutical. On behalf of my colleagues at Otsuka and Lundbeck, I want to thank the chair, members of the committee, and members of the public watching today. I'd also like to thank the patients and their families, as well as the investigators who participated in our clinical trials. You, more than anyone, know how debilitating post-traumatic stress disorder is.

Post-traumatic stress disorder, or PTSD, is a serious and often chronic psychiatric disorder. It is one of the most common mental health disorders in the U.S. and can develop after a person experiences or witnesses a range of traumatic events. Because PTSD results from traumatic events or circumstances, many may find it difficult, and even painful, to acknowledge their trauma and to seek help. And despite preconceived notions that PTSD occurs most commonly among military combat personnel, it is important to note that PTSD is most prevalent in the civilian population.

For those who do seek help, treatment options are limited. There are only two approved pharmacological treatments for PTSD in the United States, sertraline and paroxetine, both of which are selective serotonin reuptake inhibitors, or SSRIs, and were approved approximately 25 years ago. However, many patients do not experience adequate clinical response, and additional treatment options are needed to address PTSD and its severe consequences.

In the two decades since the approval of sertraline and paroxetine, many other products have undertaken investigational programs for the treatment of PTSD, but none thus far have been approved. This is, in part, due to the difficulties of conducting these trials.

As such, we are here today to discuss our supplemental application for brexpiprazole for use with sertraline for the treatment of PTSDs in adults. The targeted daily dose of brexpiprazole is 2 milligrams a day plus sertraline 150 milligrams a day. The maximum recommended

dosage of brexpiprazole is 3 milligrams a day plus sertraline 200 milligrams a day.

Brexpiprazole is currently approved for three indications. It was approved by the FDA in 2015 for the treatment of schizophrenia and as an adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults. In December 2021, brexpiprazole was approved in the United States for the treatment of schizophrenia in adolescents, and most recently in 2023, the FDA approved brexpiprazole for treatment of agitation associated with dementia due to Alzheimer's disease.

Brexpiprazole has been approved in more than 60 countries worldwide, including the European Union and Canada. Through 2023, the data cutoff date for this supplemental marketing application, we estimate that there are almost 1.7 million patient-years experience with brexpiprazole from clinical trials and postmarketing experience.

Let me take a minute to highlight how

brexpiprazole works in PTSD. PTSD is associated with abnormalities of norepinephrine, serotonin, and dopamine systems. Sertraline at clinical doses used is a selective serotonin reuptake inhibitor. Brexpiprazole is a partial agonist at dopamine D2 receptors and serotonin 5-HT1A receptors, and an antagonist at serotonin 5-HT2A receptors and norepinephrine alpha-1A, alpha-1B, an alpha-2C receptors.

Given the distinct mechanisms of these medications and prior experience with treatment in MDD together with antidepressants, we theorize that brexpiprazole in combination with sertraline would have added benefit in PTSD compared to sertraline alone.

With that background, let me review the clinical program and key regulatory interactions related to our supplemental NDA.

The brexpiprazole PTSD clinical development program for the combination of brexpiprazole and sertraline consists of three completed 12-week multicenter, randomized controlled, double-blind

trials. This is the largest PTSD program conducted to date, with more than 1200 adults enrolled. All trial centers were located in the United States. We conducted one phase 2 trial, Trial 061, a 4-arm multifactorial flexible-dose trial.

In 2019, we met with the FDA for an end of phase 2 meeting where key trial design elements for the phase 3 program were agreed upon with the agency. Two phase 3 trials, Trial 071 and 072, were conducted concurrently. These two trials were identical, except 071 was a 2-arm, flexible-dose trial and 072 was a 3-arm, fixed-dose trial. In 2024, we met with the FDA for a pre-sNDA meeting, and the submission was filed and accepted for review in April 2024.

Overall, the totality of data from the brexpiprazole PTSD clinical development program supports positive benefit-risk profile for brexpiprazole in combination with sertraline for the treatment of PTSD in adults. With only two approved treatments by the FDA in the past 25 years, both with modest and inconsistent

efficacy, and managing PTSD symptoms across all symptom clusters, many people living in the United States continue to suffer from PTSD and its severe consequences.

In the largest program in PTSD conducted today, combination treatment with brexpiprazole plus sertraline was more effective in relieving symptoms of PTSD than sertraline alone in two of three trials. Importantly, the combination treatment was generally well tolerated and the safety profile is consistent with the large database of brexpiprazole from clinical trials and extensive real-world usage in a variety of psychiatric disorders.

If approved, brexpiprazole and sertraline could address a critical unmet need and provides a substantial improvement relative to currently approved and off-label treatment options. We will address each of these points throughout our presentation today.

Here's our agenda for the rest of the presentation. Of note, Dr. Connor and Dr. Brady

will be joining us remotely today. We also have additional experts with us today. All outside experts have been compensated for their time and traveled to today's meeting.

Thank you, and I will now turn the lecture over to Dr. Javanbakht.

Applicant Presentation - Arash Javanbakht

DR. JAVANBAKHT: Good morning. I'm Dr. Arash Javanbakht. I'm a psychiatrist and Director of the Stress, Trauma, and Anxiety Research Clinic at Wayne State University. I've spent most of my career doing research and clinical work with diverse groups of civilians, refugees, survivors of torture, and first responders with PTSD.

I've also trained thousands of healthcare providers across the country about PTSD and its treatments, advised national scientific communities and organizations, and I've educated many in the public sphere about trauma via the media. I'm pleased to be here today to discuss this important topic.

PTSD is a very common psychiatric disorder. About 13 million U.S. adults every year experience this illness and about 6 in 100 people will have PTSD during their lifetime in this country. PTSD is almost twice as common among females as it is among males, and importantly, those aged between 30 and 59, which is the most productive age for an adult, have the highest prevalence of PTSD.

While historically PTSD was seen mostly as a condition of combat-exposed veterans, it's important to note that 86 percent of people with PTSD are actually civilians. Overall, PTSD leads to $232 billion in economic burden annually in the United States.

So what is PTSD? PTSD is a condition that occurs after exposure to a horrible traumatic experience. Let me give you an example.

A Detroit police detective was sitting across from me in my office, in tears, completely overwhelmed with anxiety because 10 years ago during a shooting, she lost her partner and closest friend. A decade later, it was still living in her

body like it had just happened. For people with PTSD, basically, the brain goes to the fight and flight mode and stays there, leading to a variety of disabling symptom clusters. Intrusive symptoms are memories of trauma, nightmares, and flashbacks. This detective had terrible nightmares and flashbacks of the shooting incident almost every day and every night of the past decade, and I see this commonly among trauma-exposed populations.

Patients also avoid anything that resembles the traumatic experience, including the kind of place or time of the day that the trauma happened. In case of exposure to human perpetrated trauma, which is extremely common, it often extends to avoiding all human interactions. Negative alterations in cognition and mood basically mean that the patients are unable to experience positive emotions. People cannot enjoy what they used to enjoy and have constant feelings of guilt and shame. The detective I mentioned earlier was haunted with survivor's guilt and the shame that she lived, and her partner did not.

This brain that is in a constant state of fight and flight continues to screen for danger. Patients are on edge, they're easily startled, irritable, and they cannot sleep. These symptoms, as you can imagine, lead to significant disability and distress, and suck the joy and prosperity out of the lives of patients and that of their loved ones.

PTSD is highly comorbid with other psychiatric conditions also. Approximately 80 percent of people with PTSD, which by itself is a highly disabling condition, also suffer from other psychiatric disorders such as depression, anxiety, and substance use disorders. In my experience, many people with PTSD self-medicate with street drugs, for example, in hope for a night with a few hours of sleep and no nightmares.

And as I mentioned earlier, people with PTSD avoid certain situations because of their trauma. They cannot go to their kids' games. They cannot go to any family function. They cannot go to a bar or restaurant. They are off work for a long time.

Because PTSD impacts the sympathetic nervous system and other bodily mechanisms, it leads to increased risk of cardiovascular disease, metabolic disorder, and chronic pain.

Suicide rate is high. More police officers and veterans die to suicide than they die on the line of duty. Overall, PTSD is associated with a 47 percent increase in mortality. So you can imagine, what is the enormous public health burden on the person, on the society, on the family members, and on their jobs?

Major treatments recommended in the guidelines include psychotherapy and pharmacotherapy. Over the past 25 years, we have had only two FDA-approved medications, sertraline and paroxetine, but other antidepressants are also being used off label. When it comes to psychotherapies, there are barriers to access, and many patients do not have the resources for weekly therapy sessions. Experts in PTSD treatment are mostly around academic environments, making access to them limited for the majority of the patients.

Not everybody responds equally to available medications, and for SSRIs, some symptom clusters do not respond well to the medication. In fact, approximately 70 percent of patients with PTSD experience residual symptoms after treatment. And the side effects that commonly occur, we often have to change the medication, but we do not have many options proven effective.

Only approximately 20 percent of patients with PTSD who receive pharmacotherapy are on an FDA-approved medication. We often need to try other medications, many of which are off label or not strongly supported by evidence, until we may find what works for an individual patient. These include SSRIs and SNRIs; benzodiazepines, which are not recommended; other anxiolytics; alpha blockers; and antipsychotics.

As a result, patients often end up being on more than one medication to manage various PTSD symptoms. In fact, data show that 41 percent of patients receive polypharmacy in their initial treatment regimen following their diagnosis, and

despite these efforts, about 7 out of 10 patients will need to switch medications within the first two years of their treatment. The most common reason for changes in treatment are suboptimal symptom control, which I often see in my own clinic.

To close, PTSD is a debilitating, potentially lethal condition with a high prevalence of serious comorbidities. There are only two FDA-approved medications for treatment of PTSD available with modest and varied responses, and they do not optimally address all PTSD symptom clusters; and as a result, there are trial and error uses of other medications, including unapproved or non-evidence-based therapies, some of which have safety concerns or potential for dependence.

There is an urgent need for more effective FDA-approved treatment options that are evidence-based and better address patients' burdensome, heterogeneous, and complex symptoms. Thank you for your time, and I'll now turn the

presentation to Dr. Kraus.

Applicant Presentation - John Kraus

DR. KRAUS: Hello, and good morning. I'm John Kraus, Executive Vice President and Chief Medical Officer at Otsuka. I'm also a psychiatrist by training. Today, I'll review the efficacy from our three large clinical trials, showing that in pivotal Trial 071, and supportive Trial 061, the combination of brexpiprazole and sertraline demonstrated therapeutic benefit seen through clinically meaningful and statistically significant reductions in PTSD symptoms beyond those seen with sertraline alone. In Trial 072, while the effects of brexpiprazole plus sertraline were similar to our other trials, they did not separate from sertraline.

Let me review the similarities among the trials before discussing the individual results.

All three trials had similar designs. They were each 12 weeks in duration, including a 1-week double-blind placebo run-in period prior to randomization, which was followed by an 11-week

double-blind active treatment period. To reduce any potential bias, certain aspects of the trial, including the placebo run-in period, were blinded to patients and trial personnel.

With a few exceptions, enrollment criteria were consistent across trials. Each trial enrolled patients 18 to 65 years of age with a diagnosis of PTSD as defined by the DSM-5 and confirmed by the Mini International Neuropsychiatric Interview or the MINI. Patients were required to have been symptomatic for at least 6 months prior to screening and to have had a CAPS-5 total score greater than or equal to 33 at screening and day 0 to be considered for enrollment.

The index traumatic event that led to the development of PTSD was required to have taken place within the 15 years prior to screening for Trial 061 and within 9 years prior to screening for Trials 071 and 072. No trauma types were excluded.

All three trials had the same prespecified primary endpoint, change from baseline, or week 1, to week 10 in the Clinician-Administered PTSD Scale

or CAPS-5 total score. The CAPS-5 is a clinician-reported outcome measure completed by a structured interview by rigorously trained and certified interviewers. It was designed to assess the severity of 20 PTSD symptoms, each on a scale of 0 to 4. The CAPS-5 has been used extensively and is extensively validated with good internal consistency, inter-rater reliability, and test-retest reliability.

All three trials included similar endpoints that assessed overall symptoms, individual symptoms, and function, based on both the clinician's and patient's assessment. Clinician assessments included the key secondary endpoint of CGI-S, or the Clinician Global Impression Severity Score, as well as core symptoms CAPS-5 cluster subscales. Patient assessments included the key secondary endpoint of B-IPF or the Brief Inventory of Psychosocial Function; the PCL-5 or the PTSD Checklist for DSM-5; and the HADS, which is the Hospital Anxiety and Depression scale.

Let me now go into the individual trial

results, starting with Trial 061.

Trial 061 was a 4-arm, multifactorial, double-blind, double-dummy, flexible-dose clinical trial. The primary objective of this trial was to investigate brexpiprazole as monotherapy or as a combination treatment with sertraline in adults with PTSD. Patients were randomized 1 to 1 to 1 to 1 to receive either brexpiprazole plus placebo; brexpiprazole in combination with sertraline; sertraline plus placebo; or placebo plus placebo. For the remainder of the presentation, we will refer to all arms as brexpiprazole; brexpiprazole plus sertraline; sertraline and placebo, respectively.

As noted in the FDA's briefing document, the agency has raised some statistical considerations regarding Trial 061. Let me take a moment to walk you through exactly what was prespecified in the protocol and the statistical analysis plan or SAP.

The initial protocol specified three comparisons in hierarchical testing order: one, brexpiprazole plus sertraline versus placebo; two,

brexpiprazole versus placebo; and three, brexpiprazole plus sertraline versus sertraline. In the protocol amendment, we added a clarification statement that additional testing might be added and that the order of testing would be subject to change. Importantly, language was also added that the SAP would have the final call on the testing procedure.

The SAP was finalized prior to database lock and unblinding, and was submitted to the FDA with the end of phase 2 materials. The SAP included five prespecified comparisons of interest without hierarchical testing procedure; however, to reduce the risk of not being able to test the combination versus other treatment arms, the order of testing was rearranged in the SAP. These changes were made based on the hypothesis that the brexpiprazole combination treatment with sertraline would be more effective in treating the symptoms of PTSD than monotherapy treatment, given its mechanism of action and the clinical synergistic effect between brexpiprazole and SSRIs that had been observed in

other indications like MDD.

The statistical analyses followed the SAP, and pairwise comparisons were compared with a two-sided alpha of 0.05 without controlling for the study-wise type 1 error. We also conducted a number of prespecified sensitivity analyses to assess robustness of primary endpoint results under missing at random assumption.

The primary efficacy analysis population in Trial 061 was the full analysis set, which included all patients who are randomized, received at least one dose of trial treatment, and had a baseline assessment and at least one post-treatment assessment. This slide represents the overall patient disposition in the trial. The majority of randomized patients completed the trial.

Patient demographics were generally balanced across treatment groups and were representative of the intended PTSD population. The mean age was approximately 39 years, and patients were predominantly female and white. On average, it was between 6 and 7 years since the index traumatic

event. Between 35 percent and 38 percent of patients had previous psychotherapy and between 35 percent and 49 percent had previous pharmacotherapy. At baseline, patients had mean CAPS-5, CGI-S, and PCL-5 total scores that were similar across treatment groups and representative of moderate to severe PTSD severity.

Here, we see the results of the prespecified MMRM analysis for the primary endpoint, the change in CAPS-5 total score from baseline, or week 1, to week 10 in each of the four treatment groups. The primary objective of this trial was to investigate brexpiprazole's monotherapy or as combination treatment with sertraline in adult subjects with PTSD.

In Trial 061, the combination, shown in light blue, outperformed brexpiprazole alone, sertraline alone, and placebo, with a statistically significant difference between placebo at week 6, 10, and 12. This observation is consistent with results in other indications such as the synergistic effect of brexpiprazole and

antidepressants that are seen in major depressive disorder.

We also conducted several prespecified sensitivity analyses to check the robustness of the conclusions to missing data. As FDA mentioned in their briefing book, the missing at random assumption was met and the model estimates and effect sizes may be considered unbiased. Multiple secondary endpoints further support these results. The change from baseline in CGI-S was consistent with the CAPS-5 total score results.

Moving forward, we will focus on the comparison of the combination of brexpiprazole and sertraline versus sertraline alone.

Here, when we look at all the other secondary endpoints, the combination of brexpiprazole plus sertraline shows benefit compared to sertraline alone. In addition to the effects seen on the clinician's Global Impression of Severity, further support for the efficacy of brexpiprazole plus sertraline was observed in 3 out of 4 of the CAPS-5 subscales and on the

patient-reported PCL-5, as well as the HADS anxiety and depression subscales.

Turning now to our phase 3 trial, 071, Trial 071 was a 12-week, multicenter, double-blind, randomized 2-arm trial. After screening in a 1-week, double-blind, placebo run-in period, patients received either a flexible dose of 2 to 3 milligrams of brexpiprazole plus a fixed dose of sertraline 150 milligrams or a fixed dose of sertraline 150 milligrams plus placebo.

For Trials 071 and 072, the full analysis set for enriched patients was used, which we will refer to as the efficacy sample. Enriched patients criteria were defined as those with a CAPS-5 total score of greater than or equal to 27 at the randomization visit, or week 1, and an improvement in terms of reduction in the CAPS-5 total score of less than 50 percent at the end of the placebo run-in phase; in other words, from day 0 to randomization visit week 1. This was done to exclude potential placebo responders from the primary analysis set.

In Trial 071, 416 patients were randomized to treatment, 214 patients were randomized to brexpiprazole plus sertraline and 202 in the sertraline alone group. In the brexpiprazole plus sertraline group, 77 discontinued, 137 completed the trial, and 149 were analyzed for efficacy. In the sertraline alone group, 89 discontinued, 113 completed, with 137 analyzed for efficacy.

Patient demographics were balanced across the treatment groups. The mean age was approximately 37.5 years. The majority of patients were female and white. The average time since the index trauma was 4 years. Thirty-seven percent of patients in the brexpiprazole plus sertraline group and 29 percent of the patients in the sertraline alone group received previous psychotherapy, and 29 percent in the brexpiprazole plus sertraline group and 25 percent in the sertraline alone group received previous pharmacotherapy. Baseline efficacy scale scores for the CAPS-5C, CGI-S, B-IPF, and PCL-5 were generally balanced between the treatment groups.

Trial 071 met its primary endpoint, providing statistically significant and clinically meaningful evidence that the combination of brexpiprazole plus sertraline is superior to sertraline alone. The treatment difference compared to sertraline alone at week 10 was minus 5.59 with a p-value of 0.007. Similarly to Study 061, we performed a number of prespecified sensitivity analyses for missing data. The conclusions were robust to missing data, and as FDA mentioned in their briefing book, the missing at random assumption appears to be met.

Brexpiprazole plus sertraline also demonstrated a statistically significant improvement compared to sertraline alone on both of the key secondary efficacy endpoints of the CGI-S and the Brief Inventory of Psychosocial Functioning or B-IPF. The treatment difference in the mean change on the clinician-reported CGI-S total score from week 1 to week 10 was 0.47 with a p-value of 0.0019. Consistent with the primary endpoint, benefit was seen starting at week 4 and persisting

to week 12.

For the patient-reported B-IPF total score, the treatment difference of the mean change from baseline to week 12 was minus 12.03, with a p-value of 0.0016. As we heard earlier, functional improvements are clinically important for patients with PTSD.

Consistent with the CAPS-5 results, patients treated with a combination of brexpiprazole plus sertraline reported reductions in their PTSD symptoms compared to sertraline directly, alone, on the PCL-5 scale. The PCL-5 scale is often used to record and follow PTSD symptom severity in clinical practice.

All secondary efficacy endpoints support the primary results. Brexpiprazole plus sertraline was more effective than sertraline alone on each of the CAPS-5 symptom clusters and patient-reported outcomes. These results also replicate the findings of Trial 061 on both primary and secondary endpoints, providing further credibility to the reliability and replicability of Trial 061 as an

adequate and well-controlled trial.

I'll now review Trial 072.

Trial 072 was similar to 071, with the exception that Trial 072 was a fixed-dose study of brexpiprazole 2 milligrams plus sertraline 150 milligrams, brexpiprazole 3 milligrams plus sertraline 150 milligrams, or sertraline 150 milligrams plus placebo. Similar to 071, most patients completed the study, and demographics and baseline efficacy scales were balanced across all treatment groups.

In Trial 072, neither of the brexpiprazole doses assessed as part of combination treatment demonstrated statistical separation from sertraline alone in the primary endpoint. The response observed in the sertraline alone group was higher compared to Trials 061 and 071; however, the change from baseline observed in the brexpiprazole plus sertraline arm was consistent with that observed in Trials 061 and 071.

Moving next to the secondary endpoints of CGI-S and B-IPF, neither the 2-milligram nor the

3-milligram doses of brexpiprazole plus sertraline showed a difference versus sertraline alone on the CGI-S. The mean change in the CGI-S total score for both doses of brexpiprazole was similar to the sertraline group alone.

The B-IPF did show numerical improvements for brexpiprazole plus sertraline, particularly in the 3-milligram group compared to sertraline alone. We conducted post hoc exploratory analyses to investigate potential subgroup differences in response to identify potential reasons for the discordance between Trials 071 and 072; however, we were unable to identify a cause. This is consistent with FDA's own analyses.

When we look at the results in the primary endpoint across the trials, we see consistent and clinically meaningful reductions with the combination treatment. The differences compared to sertraline are significant in both Trials 061 and 071. Although Trial 072 did not meet its primary endpoint, the absolute change from baseline observed in the brexpiprazole plus sertraline arms

was similar across all three trials. What differed and showed more variability was the performance of the sertraline monotherapy arms.

I'd now like to introduce Dr. Jason Connor to discuss FDA statistical considerations related to Trial 071.

Applicant Presentation - Jason Connor

DR. CONNOR: Thank you, Dr. Kraus.

Good morning, everyone. Hi. I'm Jason Connor. I'm a statistical consultant and President at ConfluenceStat. I've been the Lead Statistician, collaborating on the design of hundreds of clinical trials across a wide variety of disease areas. I'm also an Assistant Professor of Medical Education at the University of Central Florida's College of Medicine.

As you've read in the FDA briefing book, FDA is concerned about the lack of a formal prespecified statistical testing procedure, and therefore, how results from Study 061 should be interpreted. All of FDA's concerns reproduced here all contribute to one key question, concern about

the type 1 error rate, meaning, what is the probability of erroneously declaring an effect when none truly exists? I'll address that in the next couple of slides.

In the prespecified SAP that was finalized and signed off prior to Study 061 database lock, the formal hierarchical testing procedure from the protocol was removed. The trial design for 061 was powered to evaluate pair-wise comparisons associated with the primary objective. And remember, the stated primary objective of Trial 061 is to evaluate the efficacy of brexpiprazole as a monotherapy or as a combination treatment with sertraline in adult patients with PTSD.

So here, we see the key comparisons of interest that logically follow from those two prespecified primary aims. While no formal multiple testing procedure was used, the two prespecified primary objectives lead to three obvious comparisons of interest, shown here with nominal p-values, meaning unadjusted p-values. The left side shows the combination therapy offers a

statistically significant benefit versus sertraline alone, an active comparator, and against placebo, whereas the right side shows brexpiprazole monotherapy did not offer a benefit statistically versus placebo.

We recognize the FDA's concerns regarding the lack of a strict control for type 1 error being prespecified, but applying the three most standard multiple testing procedures -- the Bonferroni correction, the Holm step-down procedure, and the Hochberg step-up procedure -- the combination therapy is statistically significant against sertraline alone, an active comparator, and against the placebo.

FDA listed five points for consideration in their briefing book, and their first four points, shown on the left here, really point to the key fifth concern, shown in the middle, and that's about the type 1 error of the trial, meaning is this result real?

The concern, which I agree with, is that oftentimes when a nominally significant p-value is

chosen post hoc, and then claimed to be real, replication of the trial can be unlikely, meaning the probability of a type 1 error is high. But we'd remind you that, frequently, we see post hoc changes when the prespecified primary outcome doesn't achieve statistical significance.

We've all seen cases where a prespecified primary analysis is negative, but then the sponsor of a trial or the authors of a paper focus on a subset of interest or a secondary outcome that just happened to meet statistical significance, or we see people change their primary statistical method in order to achieve statistical significance. Results like that rarely replicate in subsequent trials. And I understand FDA's hesitation to consider cases like I just described as statistically significant, but none of that is the case here.

The primary outcome, the primary analytical method, were all prespecified and conducted according to plan, and one of the two primary objectives studying brexpiprazole plus sertraline

versus sertraline alone, the topic of today's meeting, achieved nominal statistical significance against an active comparator with a p-value of 0.0106, and this was robust to missing data using a variety of prespecified sensitivity analyses.

FDA's questions about type 1 error control are really a question of, is this result real? Is this result replicable? And that concern can be addressed by the presence of a confirmatory trial. Trial 071 was designed with the same hypotheses, the same primary and secondary endpoints, and the same statistical methods.

This slide shows the results from Trial 061 and 071 side by side. This shows the primary and all secondary outcomes that were measured in both trials. Trial 061's primary results, highlighted here in the top row, were replicated in Trial 071 with a very similar effect size and replicating the statistically significant benefit. Furthermore, the two trials show consistently statistically significant effect sizes across the range of prespecified secondary endpoints and CAPS-5

individual component scores.

This consistency across not just the primary endpoint, but all secondaries, supports to me that 061 is not merely a spurious result. With the lone exception of lacking a specific alpha spending strategy, Trial 061 meets every requirement of an adequate and well-controlled trial. Given the consistency of these results, it's highly unlikely that Trial 061's conclusion is a type 1 error, which is FDA's primary concern.

Thank you, and I'll now turn the podium back to Dr. Kraus.

Applicant Presentation - John Kraus

DR. KRAUS: Thank you, Dr. Connor.

Let me now spend a moment discussing why these results are clinically relevant, focusing on three different methods: assessment of CAPS-5 symptom clusters; our prespecified responder analysis for the CAPS-5; and the meaningful within-patient change on the CAPS-5. First, in Trials 061 and 071, brexpiprazole plus sertraline demonstrated greater improvements than sertraline

alone in all four CAPS-5 subscales: intrusion; avoidance; negative cognitions and mood; and arousal and reactivity symptoms.

Now, let's consider the responder analyses. So far, we've been talking about group mean change and between group differences, but a responder analysis allows us to look at individual treatment response at the individual level. As shown in this slide, a higher proportion of patients treated with a combination of brexpiprazole and sertraline, shown in blue, achieved a response prespecified as an improvement of 30 percent or more reduction on the CAPS-5 total score compared to sertraline alone, shown in pink, in both positive trials. Notably, almost 70 percent of patients on the combination treatment were responders, according to this definition, in Trial 071.

Next, let's look at defining a responder empirically. Using an anchor-based method recommended by FDA, responders on the CAPS-5 were defined using category improvements on the Clinician Global Impression of Severity Scale, a

single-item scale that's widely familiar to clinicians and easy to interpret. When the clinician observes a 1-point category improvement on the CGI-S, this corresponds to an average 8-point reduction in the CAPS-5. When the clinician observes a 2 category improvement, this is associated with a 15-point reduction in the CAPS-5 total score.

These are the score improvements on the CAPS-5 that the individual patient would have to experience to consider the treatment worthwhile, in other words, clinically meaningful. We acknowledge that the FDA references a 10-point reduction as a potential meaningful change threshold, which sits within our range of 8 to 15.

In Trials 061 and 071, a greater proportion of patients in the combination group met the meaningful change threshold of minus 8 and minus 15 points on the CAPS-5 total score compared to sertraline alone, and the differences between the combination arms and sertraline arms were consistent in these two trials. Overall, these

results support the interpretability of the score changes on the CAPS-5 in a manner consistent with the FDA's patient-focused drug development guidance.

To close, two of our three trials were positive. Trial 071 provides statistically significant and clinically meaningful evidence in all clinician- and patient-reported outcomes that the combination of brexpiprazole 2 to 3 milligrams per day and sertraline is superior to sertraline plus placebo in the treatment of PTSD. Trial 061 provides strong supportive evidence that brexpiprazole plus sertraline is superior to sertraline alone, with results replicated in Trial 071. In Trial 072, brexpiprazole plus sertraline did not separate from sertraline alone.

Overall, there was a greater proportion of patients treated with brexpiprazole plus sertraline who met the clinically meaningful improvement threshold and a greater proportion of patients who achieved the clinical response; that is, an improvement of greater than or equal to 30 percent

reduction on the CAPS-5 total score. Taken together, the totality of evidence across three trials, multiple endpoints, and multiple analyses support the robustness of the data and provide substantial evidence of efficacy for the combination treatment in PTSD.

Thank you, and I'll now turn the presentation over to Dr. Thompson.

Applicant Presentation - Thomas Thompson

DR. THOMPSON: Good morning. I'm Tom Thompson, Vice President of Global Clinical Development Head of CNS at Otsuka. I'm also a psychiatrist by training, and we'll review the safety data, showing that brexpiprazole in combination with sertraline was generally well tolerated with no added risk.

The safety data from the PTSD clinical program is consistent with prior approved indications of brexpiprazole and consistent with the safety profile of sertraline alone. The overall safety population included patients from Trials 061, 071, and 072. The pooled safety

analysis included a total of 650 patients in the brexpiprazole plus sertraline combination arm and 447 patients in the sertraline alone arm. Safety was also evaluated in 75 patients who have received brexpiprazole monotherapy in the 061 trial with no safety concerns identified. Data from these patients are not included in the pooled analysis.

Safety results from the individual trials were consistent with results from the pooled analysis. Overall, the safety profile across all combination treatment groups was comparable to sertraline alone, demonstrating that in patients with PTSD, combination treatment with brexpiprazole plus sertraline once daily was generally well tolerated and consistent with the well-established safety profile of brexpiprazole.

One death due to accidental drowning was reported in the brexpiprazole 2-milligram plus sertraline group and one death due to toxicity to cocaine in the sertraline alone group. None of these deaths were considered treatment related by the investigator.

The types of adverse events in the PTSD clinical trials were similar across treatment groups. In the most commonly reported adverse events occurring in at least 5 percent of patients, weight increase was reported with higher frequency in the combination arm compared to sertraline alone. Adverse events of nausea, headache, and diarrhea were reported with higher frequency in the sertraline alone arm compared with the combination group.

Serious adverse events were low in frequency, with a lower incidence in the combination arm compared to sertraline alone. There were no serious adverse events that occurred in more than one patient and none were considered related to treatment.

Next, I'll review the important safety topics of interest.

Identified safety topics of interest included extrapyramidal symptoms; effects on weight; somnolence; orthostatic hypotension; dizziness and syncope; suicidality; and effects on

glucose and lipids. Except for the effect on body weight, the incidence rates of these adverse events of interest were generally comparable between the combination group and the sertraline alone group. Weight increase is a known adverse event for brexpiprazole.

In the combination group, the observed mean change in weight from baseline to last visit was plus-1 kilogram, which is consistent with the known profile of brexpiprazole as described in the product label.

In summary, brexpiprazole in combination with sertraline when started concurrently demonstrated a favorable tolerability and safety profile with no added risk to that of the treatment of sertraline alone. Adverse events were similar across treatment groups, and serious adverse events were low in frequency. The safety results are consistent with a well-established safety profile and prior approved indication of brexpiprazole for a variety of psychiatric disorders and an extensive postmarketing experience.

Thank you. I'll now turn the presentation over to Dr. Brady.

Applicant Presentation - Kathleen Brady

DR. BRADY: Thank you, and good morning. My name is Kathleen Brady, and I'm a psychiatrist and a pharmacologist. I have over 30 years experience in treating patients with PTSD, as well as designing and conducting clinical trials in PTSD, bipolar disorder, and substance use disorders.

You heard earlier today about the impact of PTSD on patients, their families, and on their day-to-day functioning and, importantly, how we need more and better treatment options. For these reasons, I'm honored to be here today to provide my clinical perspective on brexpiprazole in the treatment of PTSD.

Despite the substantial burden associated with PTSD, there have only been two approved medications in the past 25 years, sertraline and paroxetine, both of which have demonstrated only modest efficacy and don't consistently treat all four PTSD symptom clusters. This often leaves the

clinician with the difficult task of having to rely on a trial and error clinical approach that's more symptom driven rather than evidence based. This comes with its own potential problems that can prolong individual suffering.

PTSD is a chronic and disabling disorder. I'd like to discuss an example of a patient who is representative of many individuals with PTSD.

Susan is a 32-year-old woman with two children. She developed PTSD following a home invasion and robbery that took place three years ago. Her prominent symptoms at that time included intrusive thoughts and memories; sleep difficulties; difficulty concentrating; and irritability. She was started on an SSRI and had some benefit, but her intrusive thoughts and sleep difficulties persisted.

Over the next several years, she experienced some diminution of symptoms, but she recently divorced, is experiencing financial stress, and her symptoms have become much more active again. She's having trouble sleeping, feels constantly nervous,

jittery, irritable, argumentative with colleagues, and having difficulty controlling her anger. She comes back to see me, and we discuss next steps. Because her symptoms are worsening, there is a growing sense of urgency and a critical need to help this patient.

With no other approved treatment options, I'm forced to utilize a symptom-focused approach in attempt to improve her symptoms and provide some relief; however, with the brexpiprazole-sertraline combination, rather than the delay caused by this step-wise trial and error approach, the combination treatment could provide her with a safe and effective treatment, accelerate the pace of her recovery, put her on a trajectory for improved functional outcomes, and give her a chance to fully recover from this very devastating psychiatric disorder.

This is why the combination of brexpiprazole plus sertraline is an exciting option for me and other clinicians, as well as for patients who suffer from PTSD. As you heard, over

1200 individuals participated in the three large-scale trials, making this the largest clinical trial program in PTSD to date. In addition, it's very rare to see an active control in these trials, making these data even more meaningful to me as a clinician.

Patients treated with the combination of brexpiprazole and sertraline achieved a statistically significant improvement compared to sertraline alone in the CAPS-5 total score, and at an individual patient level, more patients treated with the combination achieved clinically meaningful improvement.

A 15-point reduction in the CAPS-5 total score can be life changing. It can mean improved sleep, improved interactions with others, and the ability to attend rather than avoid important events. Patients are able to be a better parent and companion, no longer triggered by unexpected noises or interactions.

In general, when I use the CAPS-5 in a clinical or investigational setting using the

current standard of care, I see much less improvement as compared to what we've seen in these trials, so achieving these thresholds with brexpiprazole plus sertraline demonstrates a remarkable reduction in patients' PTSD symptom severity.

Notably, brexpiprazole and sertraline combination also showed improvement across the four PTSD symptom clusters, something we do not typically see with the current treatment options. Positive benefits were also observed in the CGI-S, the B-IPF, and PCL-5, all important clinician and patient-rated assessments.

What is also very encouraging is that there were no new safety observations identified in the PTSD population. The incidence rates of adverse events such as somnolence; dizziness; nausea; EPS; suicidality; and metabolic effects were similar to those seen with sertraline alone, and there's no risk of abuse or addiction.

The only relevant difference between the two arms was in weight gain, which is a known side

effect of brexpiprazole. In my opinion, however, the average amount of weight gain, 1 kilogram, is small, especially when put in the context of the seriously disabling and even life-threatening condition of PTSD.

Overall, the combination was well tolerated and the safety profile was consistent with that of the approved indications of brexpiprazole and of sertraline alone. To be able to sit down with a patient when discussing taking two medications and have these safety results to rely on is not only reassuring, but it's critical.

I recognize that the panel is being asked today to vote on whether there is substantial evidence of efficacy to approve the combination treatment of brexpiprazole and sertraline, and that you're wondering what to make of the 072 results. As you consider this data, I want to emphasize just how difficult these trials are to recruit for and to conduct.

Outside of the trials with SSRIs and SNRIs, most randomized controlled trials in PTSD have

failed to separate the active treatment from placebo, much less from an active control. So I'm not surprised or discouraged by these mixed results. In fact, in the sertraline clinical program, just two of four studies were positive, which is typical of what we're used to seeing. So I am pleased by the positive results in two of the three trials, especially given the results of these trials: robust response observed across all symptom clusters. For PTSD, this is rare.

What's important for me is not the results of 072 in isolation, but how consistent the combination treatment results are across the three trials. I would be disappointed if a single negative trial with an unusually large response to sertraline obstructs our ability to discuss and assess the entirety of the data presented today for a critically important disorder for which there are significant unmet clinical needs. Importantly, the combination treatment was shown to be safe across the three trials, which is consistent with a decade of experience with brexpiprazole.

There is very little downside of treating patients with PTSD with this combination. To me, the benefits far outweigh the risks for the combination product, and warrants approval so that clinicians and patients can more effectively and quickly treat the symptoms of PTSD. The totality of evidence, including two positive trials, combined with the consistency within and across trials, show that the combination of brexpiprazole and sertraline provides clinically meaningful benefit for patients. Two trials also found significant improvement in self-reported psychosocial function.

People with PTSD have suffered unimaginable trauma and now are suffering unbearable symptoms. The symptoms are difficult to treat and challenging to overcome. That is why it's so important to work quickly while the patient-doctor report is strong, and start the combination treatment to achieve a full response, rather than wait until a patient fails or has only a partial response to monotherapy or other less effective polypharmacy, and perhaps

become so discouraged that they stop treatment altogether.

This is why I am really excited by these data and that we're finally having a breakthrough in the stagnant world of psychopharmacology. The categorical change in severity that was observed in these trials across a broad range of symptoms will truly be noticeable to the patient and their families. Thank you, and I will now turn the presentation back to Dr. Hobart.

DR. HOBART: We would be happy to address any questions the committee might have of us.

Clarifying Questions to Applicant

DR. NARENDRAN: We will now take clarifying questions to Otsuka. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with,

"That is all for my questions," so we can move on to the next panel member.

Clarifying question for Otsuka, we'll start with Dr. Ballon.

DR. BALLON: Jake Ballon, Stanford. This question is for Dr. Kraus.

I imagine that that this was one of the many different things that was evaluated in trying to understand why 072 was different than the other studies, but I was wondering if you could go to the demographics of 072. I don't think I saw that presented. In particular, I'm just curious about the percentage of patients with previous psychotherapy in 072, and if it differs at all from 061 and 071. Thank you.

DR. HOBART: Dr. Kraus?

DR. KRAUS: We do have the demographics for 072, which are presented here. In 072, the previous psychotherapy ranged from 27 percent to 34 percent among the groups. Previous pharmacotherapy was about 20 percent, so relatively balanced among those groups.

DR. BALLON: Thank you.

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

DR. DUNN: Walter Dunn, UCLA, and also a question for Dr. Kraus. I think a lot of our focus on today's presentations, or our discussion today, will be on Study 061. I am particularly interested in the baseline characteristics of that group. I want to focus on the previous history of psychopharmacology, and my question centers around how that was determined using the E-TRIP questionnaire.

Although in your slide, it seems as if there's an equal amount of pharmacology history -- and I'll be asking this to the FDA presenters -- they break it down to SSRIs and other pharmacology, and there appears to be an imbalance. So I'm curious as to how you define previous psychopharmacology history. Is that purely based off of the first component of the E-TRIP questionnaire? Then, the E-TRIP scores that were across the different treatment arms, that was in

neither of the briefing documents, but I'm wondering if you have that data for us.

DR. HOBART: Dr. Kraus?

DR. KRAUS: The prior pharmacotherapy of patients within the trials was determined using the E-TRIP interview. If you'd like, Dr. Dunn, I can call up one of our investigators to talk about any of that, procedurally.

In terms of the E-TRIP outcomes or scores, I don't have that available right now. But, in general, our previous pharmacotherapy rates across studies were fairly similar to that in the general population as well. If it's important for us to try and get those scores, I can do that.

DR. DUNN: Yes. I think, based off of the FDA's briefing document, there appears to, again, be an imbalance. Even though we don't know about treatment of resistance per se, if we use history of SSRI used as a proxy for possible treatment resistance, there seems to be a higher treatment resistance in the sertraline-only arm and the placebo arm, so if you could get that data, that

would be great.

Then, if you could speak to how the pharmacology history was operationalized; on the E-TRIP form, the first category is if any drug was used at all in the history; then, based off of that, there's a series of questions about duration, views, dose, whatnot, and then it's eventually scored. In your slide, when it says there's a history of pharmacology use, is that based purely off of the report that there's any history of use, or that it actually follows through, and it was actually scored by the investigator?

DR. KRAUS: I'll answer this in two ways. I want to just address what may be an underlying question, Dr. Dunn, whether prior pharmacotherapy had an impact on the result, and then I'll ask Dr. Purselle to speak to the logistics of administering this within the clinical trial.

So as described, we did collect prior pharmacotherapy. As you see in the top row, it represents the variable of those with prior pharmacotherapy, and the bottom row, without. What

we saw in the comparison in 061 and 071, the positive studies of the combination versus sertraline, is regardless of prior history, there was a benefit seen with the combination; although numerically, at least in 061, that was slightly greater with no prior therapy and the opposite in 071. So we conclude there did not appear to be a substantial effect on outcome based on prior pharmacotherapy.

DR. DUNN: Did you happen to do that analysis looking purely at SSRI history and not just general pharmacotherapy?

DR. HOBART: I would have to get back to you on that. We did look at the prior history. There were very few sertraline-treated patients within the study to do an assessment like that, but I can get to you after the break.

DR. DUNN: Or just any general SSRI history. It doesn't have to be sertraline.

DR. KRAUS: Understood.

Dr. Purselle?

DR. PURSELLE: I'm Dr. David Purselle. I'm

a board certified psychiatrist with over 25 years of clinical and research experience. I have worked in a variety of different settings, including inpatient/outpatient and VA settings, and I was also principal investigator on all three of the trials that we're talking about today.

With regards to the administration of the E-TRIP, this was something that, first, all raters who were approved to administer, they had to meet certain qualifications in order to be approved, and then there was a didactic session in order to train on the appropriate administration and scoring of the E-TRIP. The E-TRIP was then administered via the instrument and the administration instructions, and then we did score each of the different items to get the overall score on the E-TRIP.

DR. DUNN: So for someone to fall into the category of prior pharmacology history, did that use of that particular medication have to be scored, or was it just that the patient endorsed that they had any history of use?

DR. PURSELLE: So if they had a history of

use, and it met with the guidelines within the E-TRIP, then it was identified as something that was prior pharmacotherapy.

DR. DUNN: Thank you.

DR. NARENDRAN: The next question, Dr. Coffey?

DR. COFFEY: Yes. This is a question for, I guess, Dr. Kraus or Dr. Connor. It's a subtle point I wanted to clarify because I think the 061 multiplicity issue is going to be a key topic of discussion.

On slide 53 in Dr. Connor's presentation, there was a point that that represented the three major comparisons of interest, but on slide 28, it was clarified that in the final SAP, it was actually modified to have five comparisons, which is a minor point but important in terms of the issues of multiplicity. So was it three or was it five?

DR. HOBART: Dr. Kraus?

DR. KRAUS: So there were five comparisons, but the comparison of interest that were the

primary comparisons were the assessment of brexpiprazole arms compared to the various other groups, so placebo, sertraline, brexpiprazole alone. So the combination therapy was the key aspect of interest within the study, as shown on the left side of this slide.

DR. CONNOR: Yes. If I may -- this is Jason, Dr. Connor -- to answer Dr. Coffey's question, even if we would apply, for example, the Hochberg correction or the Holm procedure to all five, the two key comparisons -- the combination therapy versus placebo, the combination therapy versus sertraline alone -- all achieved statistical significance. And even the Bonferroni correction, it would be unlikely you would put that fifth one, sertraline versus placebo, because that's a comparator drug versus placebo. So even the four on the left, those comparisons, even Bonferroni would all hit because that critical value would be 0.0125.

So I agree with you that is key, but like I said, all five here, even with Holm and Hochberg,

hit, and even the four on the left, which are key because they include brexpiprazole, would be significant by Bonferroni, which is, frankly, even rarely used anymore in pharma.

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

DR. BLOCK: Hi. This is Laura Block, the patient advocate. My first question isn't really directed to any particular person. These were some pre-meeting reading questions that I had.

In pharmacy school, back when SSRIs were used just for depression, we were told that it could take up to 8 weeks to get the full benefit. This newer data suggest, or I found online, that it can take up to 12 weeks for the more serious conditions, such as PTSD, to get to full benefit, especially with regards to Study 072. Of course, there was no way to look at that ahead of time.

But, really, why did these studies -- you were at the full dose for 6 to 7 weeks. Is there any reason maybe that they weren't longer?

DR. HOBART: Dr. Kraus?

DR. KRAUS: So the studies were designed to assess, in general, the acute effects of the combination versus sertraline alone in treatment of PTSD. As such, in similar to other trials of daily dosing, the duration of 12 weeks total was selected. Additionally, as mentioned earlier, the primary endpoint blinded to investigators was at 10 weeks.

So we believed that the combination of treatment versus sertraline would need to show benefit early in order to help guide clinicians. And as we look at the primary endpoint in 071, for example -- and I'll ask Dr. Brady to comment on her view of the clinical relevance of this -- when we look at the combination versus sertraline alone, we do see a separation beginning numerically as early as week 4, and then a statistically significant change at 6, 10, and 12 from an active treatment.

Dr. Brady, could you comment on the difference in slopes between these outcomes, please?

DR. BRADY: Yes. Thank you. Considering

just how disabling and painful the symptoms of PTSD can be for patients, it's critically important that we treat them as quickly with an effective treatment as we possibly can.

So I think the fact that the combination treatment has a more rapid onset of action is very important because during the time when people are waiting for their treatment effect, their dysfunctional or damaging behaviors can become even more exaggerated. So they may turn from avoidance to being completely housebound. They may turn to drugs and alcohol to help them sleep at night or to deal with daytime anxiety and irritability. They also can become very discouraged and even drop out of treatment.

So, to me, as a clinician, this rapid response is an incredibly important facet of this combination treatment. Thank you.

DR. BLOCK: Thank you.

One other question that I have -- and this is still Laura Block -- is I understand that you all looked at pre-study, non-pharmacological

therapy such as therapies like CBT and such. Was there any assessment? Were people allowed to -- were they required to stay where they were with non-pharmacological therapies or was there any control of non-pharmacological therapies during the trial?

DR. HOBART: Dr. Kraus?

DR. KRAUS: Dr. Block, if a patient had been on psychotherapy prior to entering the trial, as long as the expectation was the frequency, and type of therapy would not change during that 12-week period of study, the patient was able to maintain that psychotherapy outside of the trial.

Does that answer your question?

DR. BLOCK: It was an expectation, but it wasn't codified in the trial?

DR. KRAUS: It wasn't necessarily an expectation that they be on psychotherapy to be in the trial. We did assess whether patients had prior psychotherapy to entering the trial to understand whether or not that could have an impact on the result. I don't know if that's a question

you're getting as well.

DR. BLOCK: I guess what I'm looking at is I'm looking, with 072, it's not that we didn't see a response. It's that everybody responded is what it looks like. So I guess my question was, do we know for sure that people, say, on placebo didn't change therapies for non-pharmacy type therapies?

DR. HOBART: Right. The patients were disallowed to make any changes during the course of the trial, and that would have been a protocol violation. But, of course, for all studies, we collected their prior psychotherapy history and, broadly, did not find a difference in those who had prior psychotherapy versus those who did not in terms of seeing the benefit of the combination over sertraline alone.

DR. BLOCK: Great. Thank you very much. That's the end of my questions.

DR. NARENDRAN: The next question is a video participant, Dr. Raskind.

DR. RASKIND: Thank you. Relevant to my practice in the VA, I noticed, though these slides

weren't shown, that there was a very low percentage of combat trauma or war zone exposure participants among the samples in these studies. Were there VA sites involved in these trials, and is there any explanation of why there was such a low percentage of combat trauma of PTSD?

I say that [inaudible - 2:02:43] somewhat controversial event of -- there are differences in PTSD, pharmacologic and psychotherapeutic response, in a combat trauma of PTSD versus usually a single event, although not always civilian trauma PTSD. Thank you.

DR. HOBART: We did have VA sites within the program. We had two VA sites in our 061 trial and we had one VA site in our 072 trial. There were some barriers to inclusion of numerous VA sites into these trials mostly due to the fact of the electronic source versus the VA platform and proprietary issues there, but we were able to have three overall in the program.

DR. RASKIND: Thank you.

DR. NARENDRAN: The next question again from

a video panel member, Dr. Thomas.

DR. THOMAS: Hello. This is Patrick Thomas from Baylor College of Medicine. This question is for Dr. Kraus.

The applicant argues that an unusual sertraline response, a larger one, may have covered a significant difference that would have shown up otherwise. If you could speak to what evidence you have that that particular response is unusual, whether that's based on your own data or observation in other clinical trials and sertraline or studies related to this response. And I guess the secondary follow-up question of that would be, if so, do you have any hypotheses as to why?

DR. HOBART: I'd like to invite Dr. Kraus, followed by Dr. Brady, to address the question.

DR. KRAUS: So I think what we were describing is variability, Dr. Thomas, in the sertraline arm across the three studies. Although sertraline was included as a monotherapy in 061, as well, to really gauge the combination efficacy, we weren't necessarily surprised to see the studies

where sertraline had a lower effect versus a higher effect, given the history and registration trials of sertraline. To demonstrate this, these are the trials that contributed to the FDA approval of sertraline in the treatment of PTSD as described earlier by Dr. Brady. Two of those trials were positive and two of those studies were negative.

Dr. Brady, if you would care to comment on the sertraline response; you were an investigator in these studies, as well, using the compound clinically.

DR. BRADY: That's right. Thank you. Yes, I was the lead investigator on one of those clinical trials. It's one of the ones that were positive. But I'm very familiar with the data across the four trials, and in the time since have done several trials with sertraline and PTSD co-occurring disorders.

I can just attest to the variability in the response, really, both across studies. And even between individual patients within a study, we have seen definitely quite variable response. And some

people do have a robust response to sertraline alone. I think that's what is reflected in Study 072. Thank you.

DR. NARENDRAN: Does that answer your question, Dr. Thomas?

DR. THOMAS: Yes, that answers my question. I have no further questions.

DR. NARENDRAN: Alright.

The next question is Dr. Shiner.

DR. SHINER: Yes. Hi. This is Dr. Brian Shiner from the VA Vermont Healthcare System. I have two questions. The first is for Dr. Thompson and the second is for Dr. Hobart.

For Dr. Thompson, I understand over 12 weeks, patients gained about 2.2 pounds, and that wasn't seen as being huge. Since this is a sNDA, this drug has been around for a while. It was FDA approved 10 years ago. So I would want to know what the anticipated weight gain would be over a year, or 10 years, or a lifetime, and what effect that might have on the health of people that start combination treatment rather than trying the SSRI

first. That that will be my first question, and that would be for Dr. Thompson.

DR. HOBART: Dr. Kraus?

DR. SHINER: I'm sorry. That was a question for Dr. Thompson.

DR. KRAUS: I'm able to address that question as well. You did highlight that we have a number of long-term studies in other indications where we do have adjunctive treatment for major depressive disorder and also longer term treatments for schizophrenia.

So again, it is well understood, the overall weight gain with longer term treatment. This is from 52-week studies. On the left-hand side is the MDD long-term trials, which include adjunctive antidepressants. On the right-hand side is the schizophrenia trials. So we do see that the mean change from body weight to week 52 is an additional 3.1 kilograms for the adjunctive treatment group, and we did see that the weight increase, greater than or equal to 7 percent at any visit, was 30 percent in the the adjunctive MDD groups.

So we do see some increase in weight consistent with longer term treatment but does indeed plateau over time. These observations are consistent with the known profile of brexpiprazole.

I don't know, Dr. Shiner, if you'd appreciate any of our clinicians putting weight gain into context with treatment of the illness or if that answers your question.

DR. SHINER: It generally answers my question. So is your assumption that after a year, you wouldn't have much more than 3.1 or 6 or 7 pounds; that it would stop if you stayed on this for a lifetime?

DR. HOBART: The 52-week data is what we have, but based on looking at that data, it tends to plateau within that period. But I don't have data beyond that.

DR. SHINER: Alright.

My other question is for Dr. Hobart. Really, I think a lot of the problem here will boil down to differing views on 061. The FDA seems to feel, and their packet indicated, that there were

going to be three tests. They were hierarchical tests and that we wouldn't have gotten to the third test, which was brex plus sertraline versus sertraline alone; whereas Otsuka says there were going to be five tests, and they got to do the fifth test, and that was ok.

There just seems to be completely opposing views that change the outcome of the decision. So can you comment as to why there seems to be such differing viewpoints on what happened?

DR. HOBART: Certainly. The original protocol did prespecify the three tests, as you see them on this slide. This was the September 2016 version of the protocol. The protocol was amended, and that was the information that we showed on the next slide that I'm bringing up for you, which included these five comparisons of interest.

This was the final version of the protocol, which matched the final statistical analysis plan, which is the information that Dr. Connor and Dr. Kraus stepped through in their presentations earlier.

DR. SHINER: Yes. So maybe I'm not understanding the process. When you amend a protocol, do you amend it with your IRB? Do you amend it with the FDA? Where did you amend the protocol?

DR. HOBART: So when the protocol is updated or amended, yes, versions of that are sent into local ethics committees, IRBs, as well as the FDA. I think what the FDA was commenting on in their presentation, which I know will come after ours, so they can speak more to this directly, is their point was that they didn't receive the final SAP until after the database had been locked and the trial had been unblinded. But it's important to note that the final SAP was updated with this prespecified information before unblinding and before the analyses were run.

DR. SHINER: And is that typical? Why would you change during the course of a trial? Why would you change the plan?

DR. HOBART: I'd like to invite Dr. Kraus to further give the considerations for why these

updates were made, based on our knowledge of the compound overall and the disease state under study.

DR. KRAUS: It was primarily in order to test the combination treatment as a first intent. Part of that comes from what was shown earlier as to the differing and potentially complementary receptor profiles of sertraline and brexpiprazole. Part of it also comes from the unmet need and the desire to see if the combination could be superior to monotherapy in treating symptoms, particularly onset as well.

So those were some of the reasons why during the course of the conduct of the study, there were decisions made that the comparison was truly of interest. And, of course, we have historical data in MDD, although adjunctive, that does support that concept as well, that there can be added benefit. So that drove that comparison as being very important.

DR. SHINER: I guess your thinking is still not making sense to me because the way that the packet presented 061 was that it was four groups in

order to generate hypotheses for the two phase 3 trials. How did you change your hypotheses before the phase 2 trials were over if you needed the phase 2 trials to generate your hypotheses for phase 3?

DR. KRAUS: The hypothesis throughout the development program is really the assessment of brexpiprazole, either in monotherapy or in combination, as a potential treatment for PTSD. So that focus or that hypothesis did not alter during the course of the study. What did change was in terms of thinking about the importance of the combination comparison given our prior history in other indications and the potential for synergistic or mechanistic synergism between the two compounds. That is why when we revised the SAP, we prioritized these comparisons, particularly around the combination treatment.

DR. SHINER: So was there a new discovery about how brexpiprazole works during the course of the phase 2 trial?

DR. KRAUS: There weren't necessarily new

discoveries, but as you imagine, throughout the clinical trials we discuss, and often we'll finalize, the SAP after those discussions. So it was ongoing discussions within the company.

DR. SHINER: And how often do hypotheses change during the course of a trial?

DR. KRAUS: Statistical analyses plans do change during the course of the trial, and I can ask Dr. Song to allude to some of the reasons for that.

DR. SONG: My name is Jingli Song. I'm Executive Director in Biostatistics at Otsuka. Per our SAP, we finalized our SAP before the database lock, which we did in this case. We do change statistical -- some kind of data set over time. This is because it does not impact the study conduct, but it's more how we handle the data analysis.

DR. HOBART: Dr. Kraus?

DR. KRAUS: And again, Dr. Shiner, to get to your original question, the key interest of the study did not change from the change in the

hierarchical testing first elucidated in the protocol to the SAP. It's still of interest for us to understand brexpiprazole as a potential treatment for PTSD.

DR. SHINER: Yes. I'm really having trouble understanding if there weren't changes in the understanding of how brexpiprazole works or advances in biostats during the course of the trial, why you would need to change your SAP during the course of the trial. And this may be just a thing; I don't know. Does this happen every time?

DR. KRAUS: No, it doesn't necessarily happen every time. But in this case, with discussion among the team and among the companies, the combination of sertraline and brexpiprazole was thought to potentially be a very important comparison that we didn't want to miss.

DR. HOBART: And to further add, although it doesn't happen every time, it is not uncommon. Most protocols do get amended, and there are changes to statistical analysis plans throughout the trial. Importantly, the analyses that we

shared with you today reflect the final protocol and the final statistical analysis plan.

DR. NARENDRAN: The next question for virtual, Dr. Shaw.

DR. SHAW: Hi. Thank you. This is Pamela Shaw at Kaiser Permanente Washington. I have a question, and this could be either maybe for Dr. Kraus or perhaps even a study statistician. I'm trying to understand the primary endpoints and how we're seeing the differences between the trials, and it very much relates to this CAPS score.

My impression is that this is something that can be quite variable PTSD, the symptoms from week to week, day to day. So I was wondering, in general, that impression is 5 points, 10 points, that kind of variability, if that's within person from, say, week to week, if that's kind of normal, you could see a variation like that. And maybe that even relates to the assumption in the powering calculations. How variable is that score, just on its own, within a person?

DR. HOBART: Dr. Kraus?

DR. KRAUS: I'll ask also one of our clinicians within this study to address this.

Part of our effort in the study design to reduce that type of variability was that placebo run-in period such that if there was instability or variability in the symptoms, those patients wouldn't necessarily be part of the primary analysis set.

As you mentioned, as we look at the overall results, we see in the primary endpoint for 071, the change from baseline between two groups. I mentioned earlier the anchored clinically meaningful differences of minus 8 and minus 15, and you actually see that both curves approach those. But I want to share with you, also, when we think about the between-group changes, which we've talked about in the clinical trial, what we see on this chart is the reduction in CAPS-5 from baseline for Study 071 in the brexpiprazole plus sertraline group versus sertraline alone.

I also have represented on this the various

clinically meaningful values we derive, the minus 8 from a CGI change of 1 and the minus 15 from the CGI change of 2, and the 10 is from the FDA briefing book. Again, importantly, both groups do show a benefit in 071, and there's, importantly, a treatment group difference between the two groups.

Now remember, this slide is representing both responders and non-responders within each population, so the additional minus 5-9 points in the group comparison is really quite important as we're assessing an active comparator versus the comparison. However, that difference speaks to the population difference, including both responders and non-responders; therefore, we actually use that anchor-based approach I described to truly try to understand, within an individual patient, what was potentially clinically meaningful and whether or not the combination treatment favors that outcome as well.

So this represents Trial 061 and 071, the positive studies, showing a greater proportion of patients meet that individual change threshold, and

the prespecified response rate showed a similar pattern that, even with a difference that was statistically significant in the population means, we see in the individual, meaningless, here defined as greater than or equal to 30 percent reduction in the CAPS-5, a benefit of the combination over the the monotherapy.

Now, CAPS-5 can be variable, but we tried to control that within the setting of the trial and through randomization as well.

DR. SHAW: Thank you very much. I appreciate that. Actually, that slide that you showed -- that CM-33, I think it was, the first one you showed me -- I think it was a really nice slide. To me, and you can correct me if I'm wrong, the interpretation at the beginning of the trial in all the arms take a sudden dip.

We're calling that responders to placebo, but that's really just that statistical artifact, that when you have very variable symptoms and you require or you have to be so high at baseline, there's going to be a natural regression to the

mean.

So I feel like you've done a great job in terms of trying to think about how to distinguish more clinically meaningful dips, but I think -- you can correct me if I'm wrong -- sometimes when you're saying the phrase "responder to placebo," what you really are trying to do is separate out effects from regression to the mean, which is not really a response to placebo but just a statistical artifact that all the arms will experience because of the high cutoff to qualify to be in the trial.

Is that a fair interpretation of some portion of the drop of all arms?

DR. KRAUS: I do understand your point. This is part of the logic for including the placebo run-in period for patients that have substantial variability and also for blinding the site staff, as well as the patients to that run-in period and to the primary endpoint, to try and avoid certain expectation of biases as well.

In this study, of course, we're against an active control. So although non-specific effects

within psychiatric clinical trials can lead to objective patient improvement, the key thing is comparison between the two drugs. And again, in 061 and 071, we saw the combination outperform sertraline alone but, again, we did try to reduce that variability.

DR. SHAW: Alright. Thank you very much. That answers my questions.

DR. HOBART: And I don't know, Dr. Connor, if you wanted to provide any additional perspective from a statistical perspective.

DR. CONNOR: No. I think that addressed it well, and Dr. Shaw seems to have her question answered.

DR. HOBART: Thank you.

DR. NARENDRAN: This is Raj Narendran. I have a quick question. I saw from the FDA briefing that concurrent meds, people were allowed to stay on prazosin if they didn't change their dose. Your drug also has a high affinity for alpha-1 subtypes. Did you see if the prazosin people who stayed on it were equally distributed across 071 and 072 and

equally distributed across the two groups, responder-wise?

DR. HOBART: So we did see that the overall usage of prazosin was low in all three studies, so 1 percent or less, in the 061 and 072 trials at 1 percent, and then the 071 trial at half percent. So the impact of prazosin use within these trials likely would have been low.

DR. NARENDRAN: Thank you.

The next question is from Dr. Dunn.

DR. DUNN: Walter Dunn, UCLA. Circling back to the exclusion criteria, across your three studies, patients who were deemed treatment resistant, excluded at the opinion of the investigator, was that operationalized in the E-TRIP scores or is that purely based off of some type of clinical intuition?

Then a second part, if you're able to get those E-TRIP numbers, I would also be very interested to see how much of the pharmacology history was excluded because they did not meet that 8-week history cutoff.

In my opinion and clinical practice, I think it's hard to get patients to stay on a medication for 8 weeks if it's not working, and that would prematurely exclude them from being counted as a medication failure. And I guess based off of what I heard earlier, it had to be scored in order for it to be considered a pharmacology trial. So how many patients would have been included if it weren't for that 8-week cutoff?

So if you're able to get that, along with E-TRIP numbers, I'd be interested. And then to my first question, how was that exclusion criteria of treatment resistance operationalized?

DR. HOBART: Certainly. It was based on both the E-TRIP, which is information provided by the subject, in addition to any medical records that are available, and the clinician assessment as well. So, all information was taken into account.

DR. DUNN: And for this E-TRIP, is there a score that would have been in the cutoff?

DR. HOBART: We'll have to look into that and get back to you after the break with the other

additional E-TRIP information that you requested.

DR. DUNN: Thank you.

DR. NARENDRAN: Our last question, Dr. Coffey.

DR. COFFEY: Yes. Chris Coffey. This is really following on Dr. Shiner's conversation. If you can go to slide 28, I'm still trying to follow the logic here of the reason for the modification here, in that it added the five. But it's been mentioned, I think multiple times in the discussion, that it was intended to focus on the combination therapy.

So, what I'm struggling with is that would make more sense to me if the brexpiprazole versus placebo was taken out and the third one was added in, and those three were the main emphasis. I'm struggling with why the sertraline-placebo came in and the others were left there for five. It seems, looking at the logic as it was implemented and how it's being described, I'm having trouble understanding how those two align. It seems like there's a discrepancy that I just can't quite wrap

my head around.

Can you, Dr. Kraus, or Dr. Connor, or somebody expand on that?

DR. HOBART: Dr. Connor?

DR. CONNOR: Sure. Jason Connor here. Yes. I'll let the sponsor speak exactly to why they made the changes, but I think this isn't atypical. I think back to I believe was Dr. Shiner's question, it's not atypical to make changes from the protocol to the SAP. In fact, almost all protocols and SAPs have a standard line saying if there are minor modifications or any change from the protocol to the SAP, the SAP takes precedence, and I'm sure the statisticians on the panel are used to seeing this.

That said, too, I'll remind you that all of the prespecified analyses, the prespecified objectives, the prespecified primary endpoints, all of that are the same. None of that changed. I was assistant editor of a journal for six years, and we'd always see papers where it says this is our objective, and you get the results, and it starts talking about a subset. It starts talking about a

secondary outcome. None of that is the case here.

So the ordering of the original one I think is less standard; that it would be more standard to say, here, a set of hypotheses. We're going to test these via Holm or Hochberg, where the bar rises for all of them, but they're all sort of tested equally. That was alluded to by testing these five hypotheses. It did not specifically mention, for example, the Holm or Hochberg test. But when applied, statistical significance is reached, and the brexpiprazole plus sertraline group against placebo, and against an active comparator that is frequently used in this disease.

I think type 1 error control is very important -- I understand that as a statistician -- but I think this isn't the usual case where I've heard Scott Everson many times use the analogy that sometimes sponsors will shoot an arrow at a barn, go paint an arrow around where it hit, and go, "Look what we hit." That's not the circumstance here; prespecified outcome, prespecified analytical methods. In fact, all the

prespecified sensitivity analyses were around this endpoint.

So, again, it's not this super exploratory thing where we're shining a light on what got hit. The primary outcome and primary objective all were prespecified with prespecified sensitivity analyses on 061 around this very outcome. So could it have been more precise? Perhaps? Should we reject outcomes -- and can I see slide CO-55? -- from Study 061 that are clearly replicated, both in effect size and in statistical significance? I don't think we should.

I know in the original sertraline trials, it took four trials to get two positive trials. I've done a lot in dry eye. In dry eye, they say it frequently takes four trials to get two positive trials. Here, there are essentially three adequate and well-controlled trials, two of which replicate one another very closely.

And again, it's not just the primary outcome. We see very similar effect sizes in all the secondaries. This is all secondaries in both

trials, not secondaries we chose to show on a slide. This is all secondary endpoints that appeared in both trials, 061 and 071. We see very similar effect sizes in the primary, very similar effect sizes in the secondary, very similar effect sizes in the four subscales, in the CAPS-5 primary outcome.

So I think, can we argue the stats? Absolutely. It's gray, but I think it really comes down to the clinical question of, is 061 believable? And I think that, to me, Trial 071 replicating this so consistently really makes the results from 061 highly believable to me.

DR. COFFEY: Just one follow-up. I agree with your point that the primary endpoint did not change, but the fact that the original three tests weren't all based on the combination therapy almost seems to imply that the primary objective changed. Can you clarify what you mean when you say the primary objective did not change?

DR. CONNOR: Yes, certainly. The primary objective stayed in the protocol, and then I think

followed through to the SAP, was to test both the the monotherapy versus placebo and the combination of brexpiprazole plus sertraline versus sertraline. So that was the stated objective in the protocol, and that didn't really change.

So it was to look at both of those things. In fact, we see here, then, that the combination therapy achieved statistical significance, very highly significant against placebo, and even with a p-value of 0.01 versus the active comparator. And then, even with the solo evidence from 071, that p-value was very, very significant. The lower bound of that confidence interval is above 2, showing in the confirmatory 071 trial a very robust, strong effect size; that even that confidence interval is pretty far from zero.

DR. COFFEY: Thank you.

DR. NARENDRAN: I think, with that, we'll conclude the questions.

We will take a quick 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break

amongst yourselves or with any other member of the audience. We will resume at 11:15, so that gives 11 minutes on break.

(Whereupon, at 11:04 a.m., a recess was taken, and meeting resumed at 11:15 a.m.)

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

FDA Presentation - Roberta Rasetti

DR. RASETTI: Good morning, everyone. My name is Roberta Rasetti, and I am the primary clinical reviewer for this application with the Division of Psychiatry. Today, together with Dr. Yiming Chen from the Division of Biometrics I, I will be presenting the division's assessment, to date, of the new drug application for brexpiprazole plus sertraline.

I will start by providing a brief introduction, focusing on an overview of PTSD, the current treatment option, and brexpiprazole itself. From there, I will give an overview of the relevant regulatory history, highlighting some key issues in

discussion and how they relate to the review issues that I will present today. Dr. Chen will present the efficacy evaluation, and then hand it back to me for a brief discussion of safety issues. Following the presentations, there will be time for the committee to ask clarifying questions as well.

First, I will begin with some information about PTSD and brexpiprazole.

Post-traumatic stress disorder, or PTSD, is a disabling psychiatric condition characterized by intrusive memories, hyperarousal, and avoidant behavior following exposure to actual or threatened death, serious injury, or sexual violence. PTSD is associated with a high risk for suicidal ideation and behavior, and patients with PTSD are at high risk for developing other comorbidities, particularly mood and substance use disorders. It is estimated that PTSD affects approximately 13 million Americans, with about 3.6 percent of the U.S. population having PTSD in the past year, and there is a higher prevalence of PTSD in females.

Even though PTSD is a common disorder,

treatment options are limited. Current PTSD treatments include psychotherapy options and pharmacotherapy, with FDA-approved SSRIs recommended as first-line medication by many treatment guidelines. The most recent of these drug approvals was more than two decades ago in 2001. These treatments have limitations. The response rate for this medication rarely exceeds 60 percent. Off-label treatments are common, but data on their efficacy is limited. There remains an unmet need for additional safe and effective PTSD treatment.

The applicant is proposing the combination of brexpiprazole and sertraline initiated concurrently as a potential alternative to available monotherapy, aiming to address the limitation of existing treatments and provide a more effective option for PTSD management.

Brexpiprazole is an atypical antipsychotic thought to exert its pharmacological effect through partial agonism of serotonin subtype-1A and dopamine-2 receptors, and antagonism of serotonin

subtype-2A receptors. It is FDA approved for treatment of schizophrenia in adults and adolescents, is an adjunctive treatment of major depressive disorder in adults, and for the treatment of agitation associated with dementia due to Alzheimer's disease.

As I mentioned, the applicant submitted the present efficacy supplement for brexpiprazole in combination with sertraline for the treatment of PTSD in adults, and for the proposed treatment paradigm, the two drugs are intended to be started together. The proposed starting dose of brexpiprazole is 0.5 milligrams once daily in combination with sertraline 50 milligrams on days 1 to 7. Thereafter, brexpiprazole 1 milligram once daily is administered in combination with sertraline 100 milligrams once daily on days 8 to 14.

The proposed target dosage is 2 milligrams of brexpiprazole once daily in combination with sertraline 150 milligrams once daily, based on the patient's clinical response and tolerability. The

dosage of brexpiprazole and sertraline can be increased at weekly intervals, and the maximum recommended daily dosage of brexpiprazole is 3 milligrams in combination with the maximum dosage of sertraline 200 milligrams once daily.

I will now provide the regulatory history for this development program, highlighting some key discussions between FDA and the applicant.

The applicant initially sought advice on a proposed study to investigate brexpiprazole as adjunctive therapy to paroxetine and sertraline in adult patients with PTSD and incomplete response to treatment with either sertraline or paroxetine. The agency agreed on the proposed clinical trial population; but later, the applicant notified the agency of their decision to terminate the study, that was known as Study 14865A, for insufficient enrollment due to difficulties in identifying participants suitable for randomization to receive brexpiprazole.

Subsequently, the applicant changed the development plan from adjunctive to combination

therapy, intending to initiate brexpiprazole and sertraline concurrently without prior requirement or inadequate response to sertraline. Accordingly, the applicant submitted a new protocol for the proposed PTSD indication, Study 061.

The study was a phase 2 trial in subjects with PTSD with no prior requirement of inadequate response to sertraline or SSRIs. The objectives of the study were to generate hypotheses for the design of the phase 3 studies, and specifically to investigate the contribution of the single components, brexpiprazole monotherapy or sertraline monotherapy, to the treatment effect of the brexpiprazole plus sertraline combination therapy compared to placebo.

During the end of the phase 2 meeting that was held in May 2019, the agency provided guidance on the phase 3 development program. The applicant emphasized the change in the development goal from adjunctive to combination therapy, implying that evidence of an inadequate response to sertraline was not required for enrollment in the phase 3

studies. The agency agreed that although adjunctive treatments are typically studies in patients who have not experienced adequate benefit from a labeled monotherapy, this was not considered a requirement.

Additionally, the agency agreed on the planned phase 3 study designs. Specifically, the agency agreed that the program would include one fixed-dose and one flexible-dose trial as previously recommended by the agency; that both trials would compare the combination therapy, either fixed or flexible dose depending on the study, to a fixed dose rather than a flexible dose of sertraline; that the brexpiprazole monotherapy arm was not needed in the phase 3 studies given its lack of effectiveness compared to placebo in Study 061; and that the placebo arm could be omitted, as the key question was whether brexpiprazole plus sertraline was more effective than sertraline alone. And the agency clarified that the combination treatment would need to consistently show superiority to approved

sertraline monotherapy to show convincing evidence of efficacy.

I will now provide an overview of the studies submitted for a review for this NDA. The applicant conducted one phase 2 study and two phase 3 studies. We will refer to the phase 2 study as Study 061 and to the phase 3 studies as Studies 071 and 072.

All three studies share common features. They are multicenters all in the United States, randomized, double-blind studies with a 1-week double-blinded placebo run-in period followed by an 11-week, double-blinded, randomized treatment. All included subject adults between 18 and 65 years of age with a diagnosis of PTSD.

The phase 2 study was a placebo and active control study with four different arms, whereas the two phase 3 studies were controlled studies but did not have a placebo-only arm study. Study 061, the phase 2 study, had the following four arms: Arm 1 was a combination of brexpiprazole flexible dose 1 to 3 milligrams plus sertraline flexible doses

100 to 200 milligrams; Arm 2 included brexpiprazole monotherapy, flexible doses 1 to 3 milligrams; Arm 3 included sertraline monotherapy flexible doses from 100 to 200 milligrams; and Arm 4 was only placebo arm.

As I previously mentioned, the objectives of Study 061 were to generate a hypotheses for the design of phase 3 studies and specifically to investigate the contribution of the single components, brexpiprazole monotherapy or sertraline monotherapy, to the treatment effect of the brexpiprazole plus sertraline combination therapy compared to placebo.

Studies 071 and 072 were identical, except for the dose design. Study 071 was a flexible-dose study and Study 072 was a fixed-dose study. The comparator arm for both studies was a fixed dose of sertraline 150 milligrams with the placebo used for blinding.

In Study 071, subjects were randomized to one of the following two arms: flexible dose of brexpiprazole 2 to 3 milligrams in combination with

the fixed dose of sertraline 150 milligrams or to a fixed dose of sertraline 150 milligrams plus placebo. In Study 072, participants were randomized to one of three fixed-dose groups, the brexpiprazole 2 milligrams plus sertraline 150-milligram group or brexpiprazole 3 milligrams plus sertraline 150-milligram group or the sertraline 150 milligrams plus placebo group.

For all three studies, there was a 3-week fixed dose titration period during which no deviation from the protocol-defined titration were allowed. Subjects unable to tolerate the assigned dose during the titration period were withdrawn from the studies. After the titration period, in Study 061, dose increases could occur only at week 4 visits both for sertraline and brexpiprazole and dose decreases were permitted between the week 3 and week 6 visit, both for brexpiprazole and sertraline. As mentioned, in Study 071 and 072, the daily dose of sertraline remained fixed at 150 milligrams after week 3 to avoid confounding by simultaneous titration of both drugs.

In Study 071, brexpiprazole dose increases were permitted only at the week 4 visit and one-time dose decreases were permitted between the week 3 and week 6 visits, while in the fixed-dose study, 072, no dose decreases were permitted during the entire study and no dose increases were permitted after week 3 for the 2-milligram arm and after week 4 for the 3-milligram arm. For all three studies, no dose adjustments were allowed after week 6, so subjects unable to maintain their week 6 dose due to tolerability issues were withdrawn from the study.

The primary endpoint in all three studies was the change from baseline, week 1, to week 10, in the CAPS-5 total score; however, the efficacy analysis population differed between the phase 2 and phase 3 studies. For the phase 2 studies, the primary efficacy analysis was based on the intention-to-treat population, intended as all subjects randomized who took at least one dose of the double-blind investigational medicinal product, and had a baseline at least one post-baseline

evaluation of the CAPS-5 total score. So despite implementing a placebo run-in period in Study 061 with the intent to identify placebo responders, all subjects were included in the primary efficacy analysis.

In contrast, in Studies 071 and 072, the primary efficacy analysis was based on the enriched population. Placebo responders were randomized and included in the study to maintain a blinding; however, in contrast to Study 061, placebo responders were excluded from the primary efficacy analysis.

For all studies, study staff and subjects were blinded to the run-in placebo period, the details of the timing of randomization, and the timing of the final efficacy assessment; therefore, the three studies appeared to investigators, raters, and subjects as a continuous double-blind, 12-week treatment period with a 14-day follow-up period for Study 061 and 21 days follow-up period for Studies 071 and 072. For Studies 071 and 072, to reduce expectation bias due to the absence of a

true placebo arm, the actual list of treatment arms was not disclosed in the trial protocol.

Most inclusion and exclusion criteria were similar among the three studies. The studies enrolled only participants with at least moderate PTSD, defined as a CAPS-5 total score equal or higher than 33 at screening and baseline, and only participants willing to discontinue antidepressants.

Subjects receiving adequate doses of sertraline at the time of screening were excluded from the study, and adequate doses were defined as at least 50 milligrams daily of sertraline for a minimum of 8 weeks, and that was based on sertraline prescribing information and common clinical practice. The study also excluded participants with a current major depressive episode to prevent confounding the treatment effect with improvements in depressive symptoms.

One notable difference between the phase 2 and phase 3 studies was the time since the index traumatic event. For Studies 071 and 072, it was

less or equal to 9 years, and for Study 061, it was less or equal to 15 years.

The applicant used the CAPS-5 as their primary endpoint. The CAPS-5 is a comprehensive assessment tool that aligns with current diagnostic criteria for PTSD. It is a clinician-rated outcome measure typically used for PTSD research and is accepted in clinical trials. The study used the CAPS-5 past month version at screening and the CAPS-5 past week version at all other assessment timepoints.

In Version 5 of the CAPS, clinicians considered both the intensity and the frequency of the symptoms when assigning a rating on this scale. In all three studies, the endpoint was measured at week 10 to maintain a blinding to the time of assessment.

I will now pass the presentation to Dr. Yiming Chen to present the efficacy data from the clinical studies.

FDA Presentation - Yiming Chen

DR. CHEN: Thank you, Dr. Rasetti.

My name is Yiming Chen, and I am the primary statistical reviewer for this application. Now, I will present the efficacy analysis methods and results of these three studies.

The objective of the phase 2 study, 061, was to explore the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adults with PTSD. This study served as a hypothesis-generating study to inform the future clinical development. We would like to highlight that the statistical analysis plan of this study was submitted after data unblinding at the end of the phase 2 meeting. The applicant did not control the overall type 1 error for multiple comparisons because of the exploratory nature of the study. Instead, the clinical study report presented results of five prespecified, pairwise comparisons without adjusting for multiplicity.

The primary efficacy analysis used MMRM; that is, mixed model for repeated measures analysis. The response variable was change from baseline in the CAPS-5 total score. All scheduled

post-baseline CAPS-5 visits were included in the analysis but the primary endpoint was at week 10. The primary efficacy population was the intent-to-treat population, which included the placebo responders from the placebo run-in phase.

This slide presents efficacy results for the primary endpoint, the least squares mean change from baseline to week 10 in CAPS-5 total score. Per the statistical analysis plan, the applicant intended to compare the combination therapy, as well as the individual components with the placebo arm. In addition, the combination therapy was compared with each individual component. Please note, all p-values from this table are nominal p-values; that is, not adjusted for multiplicity.

In this table, the blue highlighted text are the results of the combination therapy compared with placebo and with sertraline monotherapy, respectively. These two comparisons indicate an estimated 6 or 5.1 point larger reduction in least squares mean change from baseline in CAPS-5 total score for the combination therapy as compared with

placebo or with sertraline. However, as shown in the red highlighted text, neither brexpiprazole nor sertraline monotherapy showed a clinically meaningful difference in CAPS-5 reduction when compared to the placebo arm.

Informed by the results of the phase 2 study, the objective of phase 3 studies was adjusted to assess the efficacy of the combination of brexpiprazole plus sertraline compared to sertraline in adults with PTSD. For both studies, the primary efficacy analysis was, again, based on MMRM, which is similar to Study 061; however, differing from Study 061, for the phase 3 studies, the primary efficacy population was full analysis set for the enriched population, which essentially excluded placebo responders from the placebo run-in phase.

Furthermore, in Study 072, to control the overall type 1 error for multiple doses compared with the control, a global test was first conducted by comparing the average effects of the two combination therapy arms with the sertraline arm.

If the global test was statistically significant, each combination therapy was then compared with the sertraline arm.

This slide presents the results of estimated least squares mean change from baseline to week 10 in CAPS-5 total score for both studies. In Study 071, results on the top, there was an estimated 5.6 point larger reduction in the primary endpoint for participants randomized to the combination therapy compared to those randomized to sertraline. The treatment difference was statistically significant. However, in Study 072, results at the bottom, there was no statistically significant difference between the average of two combination therapy arms and the sertraline arm for the primary endpoint.

These figures are the visualizations of the response trajectories for each treatment arm. The response is in terms of the least squares mean change from baseline in the CAPS-5 total score. In these two plots, we see that all arms experienced reduction in CAPS-5 total score throughout the

study. For Study 071, we observed a separation between the two curves, but for Study 072, the three curves were very close to another.

To understand the negative results of Study 072, we conducted several assessments. First, we explored the impact of the baseline demographic and clinical characteristics and found that Study 072 was generally comparable with Study 071 with small differences. For example, Study 072 enrolled more Hispanic subjects. Also, the geographic distribution in Study 072 differed from Study 071, but it was similar to Study 061.

We also conducted some post hoc subgroup analyses such as by sex, ethnicity, prior PTSD treatment, and baselines severity, but we did not detect any signals in any subgroups of the primary efficacy population. The difference between Studies 071 and 072 regarding the dosing schema -- fixed dose for Study 072 versus flexible dose for Study 071 -- does not appear to have affected the results. Study 071 and 072 had similar blinding procedures as previously

described.

The plasma levels of brexpiprazole and sertraline were comparable between studies. Additionally, the percentage of participants who discontinued due to poor compliance to treatment was similar between these two studies. In conclusion, none of these assessments could explain the contradictory results observed between Studies 071 and 072.

Given that only one of the phase 3 studies was positive, the applicant sought additional evidence from the phase 2 study to support approval. As mentioned, due to the exploratory nature of the study, the statistical analysis plan listed five pairwise comparisons without specifying a multiplicity control method. To address this, the applicant retrospectively proposed three post hoc multiple testing procedures which weigh three selected comparisons equally.

In the next few slides, we will discuss the post hoc analysis of Study 061 and our concerns.

Due to the lack of multiplicity control, no

statistical significance can be concluded from the phase 2 study. This slide summarizes the post hoc multiplicity control methods considered for Study 061. First, the review team noted that there was a multiplicity control method prespecified in protocol addendum but abandoned in the statistical analysis plan. As shown in the bottom bullet, the prespecified hierarchical testing procedure used the following order: first, combination therapy versus placebo; second, brexpiprazole versus placebo; last, combination therapy versus sertraline.

This hierarchical testing result is in the middle block of the table. Only the combination therapy versus placebo comparison would be statistically significant, at 0.05 significance level, but not the other two comparisons.

In this application, the applicant declared that there were only three pairwise comparisons that were clinically relevant to Study 061 objective, namely combination therapy versus placebo, combination therapy versus sertraline

monotherapy, and brexpiprazole monotherapy versus placebo. The applicant further considered three post hoc multiplicity control methods. These are listed in the bottom block of the table, namely Bonferroni, Holm step-down, and Hochberg step-up procedure.

As seen here, these three multiplicity control methods would lead to the same conclusion; that is, the treatment difference was statistically significant when comparing the combination therapy with sertraline or with placebo.

This is the same efficacy summary table for Study 061 as you saw earlier, but here we highlighted the three selected comparisons: combination therapy versus placebo, combination therapy versus sertraline, and brexpiprazole versus placebo.

This slide zooms into these three selected comparisons and shows how the hierarchical testing procedure prespecified in the protocol addendum would have proceeded if exercised. The bold numbers 1, 2, and 3 and the arrows denote the

hierarchical testing order. The test would start with testing the difference between the combination therapy and placebo.

The p-value is smaller than 0.05; thus, the test would proceed to the second comparison, brexpiprazole versus placebo. Because the second comparison would fail at 0.05 significance level, the testing procedure would stop, and there would be no alpha left to test the third comparison, which is the combination therapy versus sertraline.

We have some remarks on the post hoc analysis of Study 061. Study 061 protocol addendum prespecified a hierarchical testing procedure to control for multiplicity. This testing procedure was consistent with the study's primary objective, which was to assess the efficacy of brexpiprazole as monotherapy or as combination therapy with sertraline.

Specifically, the first and second comparisons in the testing order reflect the two parts of the objective. If any alpha were left, it would be used to test the third comparison; that

is, combination therapy versus sertraline. Nevertheless, in the subsequent statistical analysis plan, the applicant decided to abort the multiplicity control and instead listed five comparisons to explore before data unblinding.

Now, after unblinding of all three studies, and given that Study 072 was negative, the applicant attempts to extract information from Study 061 to support the objective of phase 3 studies, which was to assess the efficacy of the combination of brexpiprazole plus sertraline compared to sertraline. In conclusion, these post hoc analyses raise concerns about the lack of overall type 1 error control, which is crucial for demonstrating efficacy.

In the overall summary of efficacy, Studies 071 and 072 were two adequate and well-controlled phase 3 trials which were designed similarly. Both of them were multicenter trials, each with sufficient sample size to detect the treatment effect on their own. Study 071 was a robustly positive study with a very small p-value

close to zero; however, Study 072 was a clearly and convincingly negative study that showed essentially zero point treatment effect estimates on its primary endpoint.

Study 061 was a phase 2, exploratory hypothesis-generating study. Its primary objective was to determine whether brexpiprazole should be used as monotherapy or as combination therapy with sertraline. In this study, the sample size was powered to detect the difference between active arm and placebo. Although some p-values were nominally significant, we cannot conclude the superiority of the combination therapy over sertraline from this study because it was not designed to formally compare efficacy between treatment arms. It should be noted that selective reporting of the supportive results can compromise the statistical integrity of the analysis.

Following the completion and readout of phase 3 study results, the applicant retrospectively applied several multiplicity control methods for pairwise comparisons. This

raises concerns about lack of overall type 1 error control because the statistical testing results depend on choice of such methods, as shown earlier; therefore, the post hoc analysis results of this study may not provide additional efficacy evidence.

Although the estimated treatment effects of some efficacy measures in Study 061 were similar to those in Study 071, this does not address our concern about the lack of type 1 error control due to multiple pairwise comparisons within Study 061. In addition, we would like to remind you that Study 061 and 071 employed different dosing schemas and different efficacy analysis populations. Most importantly, the other phase 3 study, 072, failed to replicate the favorable results of combination therapy versus sertraline. Furthermore, the failure of sertraline to demonstrate superiority over placebo raises questions about the interpretability of Study 061.

This concludes our presentation on the efficacy. I would like to turn the presentation back to Dr. Rasetti to discuss the safety data.

FDA Presentation - Roberta Rasetti

DR. RASETTI: Thank you, Dr. Chen.

I will now move on to a review of safety. Before presenting the safety findings for this combination therapy application, let me walk you through the individual safety profile as they reported in the leveling.

On the left side, sertraline, which is already approved for PTSD, carries several important warnings and precautions that we are all familiar with. These include, for example, serotonin syndrome; sexual dysfunction; bleeding risk; and hyponatremia. The common adverse events include, for example, gastrointestinal effects like nausea and diarrhea, as well as neurological effects such as tremors and sexual side effects.

On the right side, brexpiprazole brings its own set of safety considerations. The warnings and precautions include neuroleptic malignant syndrome; tardive dyskinesia; metabolic changes; blood disorders like neutropenia and agranulocytosis; syncope; orthostatic hypotension; and seizures.

The common adverse events include, for example, weight gain, akathisia, and extrapyramidal symptoms.

The safety results from the three studies align with what we already know about these medications where they're used individually. We are not seeing any unexpected safety signals when brexpiprazole and sertraline are used together; however, although no new safety signals were identified in the development program, the evidence of benefit of co-initiation of brexpiprazole and sertraline for the treatment of PTSD should also be considered in the context of the known risks of these two drugs.

This concludes the FDA presentation. Thank you.

Clarifying Questions to FDA

DR. NARENDRAN: We will now take clarifying questions to the FDA. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific

slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "This is all for my questions," so we can move on to the next panel member.

Clarifying questions for the FDA, the first question, Dr. Dunn.

DR. DUNN: Walter Dunn, UCLA. It's a question for Dr. Rasetti.

Referring to page 46 in the FDA briefing document, along the lines what I was asking the sponsor, concerns about what appears to be an imbalance between the history of SSRI use, I don't know if this is statistically significant. I'll defer to my statistical colleagues about that, but it looks dangerously close. So we're looking at 30 percent of history of SSRI use in the sertraline group and the placebo group and 18 percent in the combination group. I noticed that this was not commented in the briefing document per se but, obviously, you pulled that apart; otherwise it

would have been buried in general pharmacology history.

How does the agency interpret that? Myself, I see that potentially as a proxy of treatment resistance. Obviously, you pulled it out for some reason. Can you discuss some of your thoughts around that?

DR. RASETTI: So you're referring to Study --

DR. DUNN: 061, yes.

DR. RASETTI: -- 061, yes.

Roberta Rasetti, clinical reviewer, FDA. We've observed there's a difference and, honestly, I'm not sure how much it is statistically significant because the numbers in each subgroup are very, very small. But one important thing to remember is that what we want to understand in this development program is why Study 072 is negative compared to Study 071. And when you compare 061 and 071 with the results that were considered in the same directionality, this data is not consistent. If you look at the SSRI distribution

in 071, it is equal across groups, so we do not believe that this has any important effect on the results.

DR. DUNN: One interpretation is that you've got a more treatment resistant population in the placebo and sertraline group, so therefore, they're not going to -- this is artificially decreasing the response, and that's why you see an improvement or an advantage with the combination treatment. You're comparing apples to oranges. That's my interpretation of potentially why 061 is a positive study.

DR. RASETTI: That would not explain why 071 is a positive study because they have a similar distribution of SSRI.

DR. DUNN: Right, exactly. So 071 has a similar distribution of SSRI use; 061 doesn't. So you have a lower prevalence of SSRI use in the combination group compared to the sertraline-only group. So my thought on this is that you've got a more treatment resistant population in the sertraline-only group, and that's why you're not

seeing a big of a response, and that's why you're seeing a statistically significant delta between combination versus sertraline only.

DR. FARCHIONE: Maybe if I can just jump in. This is Tiffany Farchione.

What it sounds like to me, Walter, what you're trying to get at is you're acknowledging that, yes, the prior treatment isn't something that differentiates 071 from 072, and I think we all agree on that. So now you're looking at 061 and trying to make sense of it in a way that can help you decide whether that can provide some additional data. And looking at 061 and seeing that sertraline also didn't separate from placebo, you're trying to understand -- it's the interpretability question that we've kind of raised but maybe is getting lost in the statistical discussion.

If you have brex plus sertraline, and you compare it to sertraline, and it wins, that's great. But if sertraline didn't beat placebo, what does it mean? So you're looking for similarities

between the placebo and sertraline group that maybe aren't present in the combination group.

And I can appreciate that attempt to try to identify something, and I think that that is definitely one of the questions for today in terms of, if we're going to try to use 061 to support a conclusion on efficacy for the combination, how do we have to look at that data to explain those unexpected findings, like the unexpected finding that a drug that is approved to treat PTSD didn't beat placebo in that context?

So I think it's a really valuable question. I'm just not sure that we actually have an answer for that.

DR. DUNN: That's fine. Yes, you encapsulated my question perfectly and probably better articulated than me.

Then a follow-up question against Study 061, notice that at week 12 -- not from the FDA's presentation, but from the sponsor's -- for 061, there's actually no longer any statistical separation from the sertraline-only group. So is

there any concern about the durability of the effect?

I acknowledge that, best-case scenario, there's a more rapid acting effect of the combination, but if you lose it, or sertraline catches up, what's the utility of the treatment? I'm just curious if that's something that the FDA considered, looked at? It wasn't in your briefing document, but this was shown in the graph from the sponsor.

DR. RASETTI: Yes. Roberta Rasetti, FDA. In Study 061, we did look at week 10, and there was no difference. If you look at week 12, still it's not a significant difference, but there is a trend. The PTSD studies for sertraline were at week 12, the one for the development program of sertraline for PTSD.

DR. DUNN: Thank you.

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

DR. SHINER: Hi. My name is Brian Shiner. I'm from the VA Vermont Healthcare System. This

question is for Roberta Rasetti.

I understand there was an end of phase 2 meeting between the VA [sic] and Otsuka. They brought a new SAP, which they had not submitted to you yet but which they used after they unblinded the data -- which they put in place before they unblinded the data, and then used to look at the data, with the five comparisons.

My understanding, then, would be that when they came to the end of phase 2 meeting, they would have had one trial already with convincing evidence that brex plus sert was better than sert alone. So it would seem unusual to me that they would then do two phase 3 trials. Why wouldn't they have just done one phase 3 trials if they already had one positive trial?

DR. FARCHIONE: This is Tiffany Farchione. I'll go ahead and take that, because I was in the room and Roberta wasn't.

I think it's important to understand we're looking at everything with hindsight being 20/20 and everything. The phase 2 study was intended to

be exploratory, and it was intended for the company to decide, do we want to go for a combination? Do we want to try to go for brexpiprazole alone for treatment of PTSD? Are we doing adjunctive? Are we doing it together? They were answering a lot of questions. So it's the idea that, yes, the analyses were prespecified, but it's the multiplicity that wasn't.

That's fine in that context. It's intended to help design the more definitive, adequate and well-controlled studies, the phase 3 studies. It all made good sense at the time. And we're looking at this, and we're like, we did have some concerns about sertraline not beating placebo in the phase 2 study, and what does it mean? But ultimately, if both of those phase 3 studies had shown that the combination beat sertraline, we wouldn't even be here today. We'd be done.

So the trouble comes in where now we've got these discordant results, and we know we had something in that exploratory study that was definitely worthwhile to the company to say we can

go pursue this. The question for us is, from a regulatory perspective, is that enough for us to make a decision?

One of the reasons why we framed our discussion questions the way we have is because we want to understand how you guys are interpreting the data and the role of the different studies, and how you're viewing the evidence at hand, and how you interpret that in terms of both the overall benefit. Have they demonstrated benefit? Is Study 061 enough to overcome the fact that we have Study 072?

These are all things that we can take from the discussion to help us frame the benefit-risk analysis when we finalize our review. I mean, we're here today because these are difficult questions, but I want to reassure you, there was nothing like nefarious or sketchy about the way this was done, or that they're going back.

DR. SHINER: No. I think my question was somewhat rhetorical.

DR. FARCHIONE: Okay.

DR. BURACCHIO: I just wanted to make a general comment about when we can leverage phase 2 data studies. We have a typical requirement that when it is feasible to conduct two adequate and well-controlled trials, that is what we expect to establish, substantial evidence of effectiveness. There are times when phase 2 studies can be considered adequate and well-controlled trials, and we are able to leverage them as one of the two adequate and well-controlled trials. That is typically a situation where there is a prespecified statistical analysis plan with appropriate control for multiplicity.

I wasn't present at this meeting, but I suspect that at the time they came in from the meeting, this was presented as an exploratory study because there was no hierarchical control, so it wasn't considered an adequate and well-controlled study at that time. They were proposing to conduct their two adequate and well-controlled studies. It's now at this point that we're going back and considering, could that phase 2 study be considered

an adequate and well-controlled study?

DR. SHINER: Yes. You presented a very reasonable example of using phase 2 data as one of the adequate and well-controlled trials. Does this ever happen, that we say you need two phase 3 trials, one is negative, and then we go back and reinterpret the phase 2 data in order to come up with another one? This just seems unusual to me, and I just need to know -- I think it's really important Otsuka did this work. I think it's really important that there be new treatments for PTSD, but also this is important for public health. How do we know whether a drug's effective or not, given the risks of weight gain and other things?

So does this happen? Do we look back after a negative result looking forward?

DR. BURACCHIO: Yes. So I would say it's definitely not typical and would be unusual. Has it happened? It probably has. I would have to look through and come up with some other examples, but I think in the situations where we do that, it's often in a situation where it's not feasible

to conduct another trial. That's usually in rare disease settings, or if there's a really compelling result; that there's a compelling public interest to get that drug to the market, or the results are particularly convincing and persuasive in that phase 2 study, even in the absence of adequate control for multiplicity. You kind of don't even need that multiplicity control because it's so persuasive.

DR. NARENDRAN: Thank you.

Dr. Ballon?

DR. BALLON: Jake Ballon, Stanford. The questions, I guess, are really maybe for Dr. Chen perhaps. I'm trying to think about the placebo response and how placebo was presented in the failed study.

I guess the first is, I'm trying to understand how subjects understood their chance that they were going to get the control treatment versus one of the active treatments, the brexpiprazole combo treatments. It sounds like you said they were told it was the same between both

071 and 072. But is that the case, because it's one-third and two-thirds of patients who were on placebo?

DR. CHEN: Yiming Chen, statistical reviewer. I'll first address your concerns on the study blinding. We did investigate the subjects' informed consent. I believe the applicant has done a fair job in blinding, so the subjects will not know how many treatment arms are in the study, and they will not know the proportion or probability they get active arms in both phase 3 studies.

Then you asked about the placebo responders. We did look into that for both phase 3 studies because they excluded placebo responders; however, the proportion of placebo responders was not that dramatic, about one-fourth or one-third, and we have conducted subgroup analysis for those responders. Due to the small sample size, we cannot draw sound statistical conclusions, but the applicant has also conducted analysis to combine the population. They call that a full analysis set, and we observed consistent results in the

enriched population and in the full analysis set.

DR. BALLON: So then, did subjects not know that they were in a fixed-dose, 3-arm study in 072, or how was that handled? Because if I'm a subject in a study, and I see there are three arms, I assume one-third, one-third, one-third. I wouldn't necessarily assume one-half, one-half. And I just think that the placebo response is often changed by expectation bias.

DR. CHEN: Right. Yes, we considered that, and the applicant may have more details on that. But from my memory and understanding, the subjects will know they have a chance to receive either placebo or active treatment, but they have no idea about the proportion or the randomization probability, like how large is the chance they are going to receive active arm.

DR. BALLON: Then I guess the other question associated with that is trying to differentiate between how to think about a failed trial, where placebo response eliminates the potential for separation from a potentially effective treatment

versus a flat line efficacy. This is maybe for anybody at the agency. I think of it as this is a trial looking like the response was the same for the combo treatment across all three trials, and that the placebo response jumped in the failed study.

Is there a different thinking around failed studies versus negative studies, or do we not really differentiate between those two when you're presenting a success or not?

DR. BURACCHIO: It can be difficult to tell whether something is truly negative because the drug doesn't work or if there's a failure due to some flaw in the design of the study that led to a negative result. So I think we often tend not to distinguish between those, and we use the other available evidence to help us try to interpret whether something is truly negative because the drug doesn't work or whether there's a flaw. And that's why we need two studies, typically, to have that independent substantiation to make us more certain of our conclusions.

DR. FARCHIONE: Yes. This is Tiffany Farchione. It doesn't help that in psychiatry, we have a real placebo problem. It just adds another layer of complexity to trying to understand what goes on.

DR. BALLON: Thanks.

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

DR. COFFEY: Yes. This question is primarily for Dr. Chen, but others can weigh in as well. I think one of the things -- and this kind of feeds off of the prior discussion and some of the things that came up, is 061 an adequate, well-controlled study, and the conversation like the end of phase 2 discussion when it was considered more exploratory. I'm trying to clarify terminology because I think this is going to be really important for our discussion later.

It was mentioned earlier in the discussion that it is not uncommon for the SAP to change late in the study, which I completely agree with for phase 2 studies. My question for Dr. Chen is, is

it common, if something is intended to be an adequate and well-controlled study, for the SAP to change prior to FDA seeing it?

DR. BURACCHIO: If a study is intended to be serving as what we call a pivotal study to provide evidence of effectiveness for a marketing application, we would typically receive the SAP in advance and provide feedback and comments on it. That would be the usual approach, and that may not happen until later, usually often about halfway through the study conduct. But there can be some negotiations of the SAP for a pivotal study.

It would raise concerns for us if it was something that happened right before the database lock. That might raise concerns to us that there was some understanding of the data that was influencing a decision to make a change in the SAP that late in the development program. Typically, though, we do provide input beforehand. It is less usual for us, in a study that's intended to provide evidence of effectiveness, to have the SAP submitted after a study is completed. We usually

do try to provide some feedback.

DR. COFFEY: I guess my second question is more general. Based on that discussion, what I'm, I guess, trying to clarify for the future discussion is it doesn't seem to me, any way under the standard definition, 061 could be considered adequate and well controlled the way it was conducted.

Is that what we're trying to address or is the information from 061 suitable enough to be a pseudo second trial, whether it's adequate and well controlled, to support the evidence from 071?

DR. FARCHIONE: I wouldn't ask the committee to comment on whether a study was adequate and well controlled because that's generally a regulatory decision, but you are raising important points about the role of 061 in the overall program.

We also have the option that even if you wouldn't necessarily consider that to be adequate and well controlled, one positive study plus confirmatory evidence is another option for reaching a conclusion on substantial evidence of

effectiveness. It's reasonable, given the strength of the positive study with the small p-value, to also think about that. But again, that's part of why we framed the discussion questions the way that we have, so that we can get an idea of how you think about the data, generally, and what aspects of it are supportive, what aspects work against the program, and so on.

DR. BURACCHIO: This is Teresa Buracchio. I wanted to just tag on to that for a second since Dr. Farchione raised the question of this single study plus confirmatory evidence.

We do have that terminology in our regulations. It's in our guidances about establishing evidence of effectiveness, and 071 most certainly meets the criteria for an adequate and well-controlled study. The question is, when can we leverage the single study plus confirmatory evidence pathway versus the two adequate and well-controlled studies pathway?

Again, this comes back to the setting of is it feasible to do a second study? And typically,

we would look to the single study plus confirmatory evidence in a situation where it may not be feasible to do a second study, and again, that gets back to what I said before about rare diseases, compelling persuasive results, et cetera.

It does seem to us that this is an indication where it would be feasible to do a second study.

DR. FARCHIONE: They did do a second study.

DR. BURACCHIO: And they did do a second study, and it was negative. So what we have are these clear polar opposite results and a study that was not designed to be an adequate and well-controlled study. It was designed to be an exploratory study. So our question is, although there does seem to be an effect with the combination therapy in that study, is that effect persuasive enough, substantial enough, that we could overcome our concerns about Study 072?

DR. BALLON: Thanks. That's very helpful.

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

DR. SIMON: This question I think is for Dr. Rasetti or for someone else from FDA. I'm focusing on page 42 of the FDA briefing document. There's a sort of closing comment about Study 061, raising questions about the ability of Study 061 to design a treatment effect.

But I think what I've heard in this discussion is not that there was any thought that there was some fundamental design flaw in Study 061 or some failure in execution that would have reduced the assay sensitivity, or would have made Study 061 unable to detect a true treatment effect -- and as evidence, Study 061 did detect treatment effects in other comparisons -- and that causes me to think that the explanation for that finding in Study 061 was a difference in the patient population recruited, not by design or intent, but that study did somehow enroll a population of people less likely to respond to sertraline alone. I'm curious about your thoughts about that.

DR. MANTUA: Valentina Mantua. I'm

Associate Director of Neuroscience. It goes back to the question we had before. Every application is unique, and what we're seeing here in this context is that we need to demonstrate that adding up the two drugs concurrently, it has an effect that is superior to currently available monotherapy, and there were two studies designed to see that.

If we had a trend or something in Study 072, we could be able to leverage even that, or some understanding, but we have no evidence of that superiority. So looking back at Study 061, we have a number of questions, one of which is why hasn't sertraline separated from placebo, and is it positive only because -- and that goes back to Dr. Dunn's questions as well, where he hypothesized some kind of resistance that's higher in that. But given that arm has not separated from placebo, how do we interpret evidence of superiority of the combination over an arm that hasn't separated from placebo?

So we have a number of interpretability

problems with Study 061 that raised the concern, are these data sufficient to overcome a flat negative study that was adequate and well controlled? It's different ways of saying the same thing, but in the context of superiority.

DR. SIMON: Thanks.

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

DR. SHAW: Yes. Thank you. Pamela Shaw. I do have a clarifying question. I heard a member of the FDA recently saying, sometimes there's this fine line between whether the study is considered negative, truly negative, or a failed study. And one way to think about that statistically is when we look at the statistical evidence, do we have statistical evidence to interpret the null hypothesis?

Everything we heard today, these are all well-conducted trials with the missing data, the protocol, and it seemed very excellent, rigorous methodology. One thing we did not hear about -- which helps me think about the negative

Study 072, and as FDA mentioned in this recent discussion, that had that been positive, we wouldn't be here. Did anyone retrospectively go back to the power calculations from the point of view of the power to reliably detect the difference between arms?

One of the things it relies on is the variability in the change, which is your primary endpoint, the variability of that primary endpoint. Was there any evidence after the trial was done that that was actually more variable for whatever reasons, this patient population that happened to be recruited? Was it more variable than expected or was it within the design considerations? I wonder if the FDA had looked at that since this was your clarifying question session or if somebody knew the answer to that question?

DR. CHEN: Yiming Chen, statistical reviewer. Can we bring up FDA slide number 27?

First, for the power calculation for both phase 3 studies, they were based on the same assumptions for treatment effects and the variation

of the treatment effects. So each of them should be powered to detect the treatment difference between the combination and the sertraline, and we have no issue with that.

If you look at the mean at baseline and the standard deviation of the CAPS-5 total score, we would think the CAPS-5 total scores are pretty balanced at the baseline. And also for the estimation, we didn't observe significant difference between the standard errors of the primary endpoint estimates.

DR. SHAW: Thank you. This is a perfect slide. That standard error, which is about 1 in each arm, what was the design consideration? You had to assume a value for that standard deviation. Was it something close to 1, or bigger than 1, or is it something less than 1 in the standard power calculations?

DR. CHEN: The applicant may have that information, but what I recall is we assumed a much larger standard deviation, standard error.

DR. SHAW: Okay. That's great. That's the

nature of my question because that tells you not that they're the same in the two arms, but that you can interpret the null because you had good power because you were within the design considerations. And the applicant, I guess, would know best about this.

DR. CHEN: Yes. I do believe these two phase 3 studies are designed very similarly.

DR. SONG: This is Jingli Song. We assumed exactly the same assumption for both 071 and 072. The standard deviation is assumed 14 for both studies. The treatment difference is 5 points.

DR. SHAW: The standard deviation for a single measurement or for the change?

DR. SONG: The standard deviation within arm, not the difference.

DR. SHAW: Okay, not the difference. Okay. So that's maybe not -- what you necessarily need to understand the power. But I'll think about that. I'll say it's probably enough for me. Thank you.

DR. NARENDRAN: Thank you.

The next question, Dr. Dunn.

DR. DUNN: Walter Dunn, UCLA. In the briefing document, you noted that both of these treatments are already FDA approved for treatment of depression, and I know that one of the exclusion criteria was not meeting DSM criteria for MDD. But if you look at the HADS-D scores, they're essentially clinically significant, minus 10, minus 11. This is designated as a clinically significant mood, or episode at least. And there are a variety of reasons why people don't meet criteria for MDD on a SCID or DSM, but clinically we say this is a major depressive episode.

So I'm wondering how important is it for the agency to disentangle the antidepressant effect of these treatments versus actual core PTSD benefits. And we know there's a huge overlap. We have patients who their depression gets better on a treatment, and many of their core PTSD domains get better. So I'm just wondering how you're interpreting that exclusion criteria as adequate in actually excluding a patient with a major depressive episode.

DR. FARCHIONE: Yes. This is Tiffany Farchione. I think the exclusion criteria, we were satisfied with those. If we look at the HADS scores and things like that, they're pretty balanced across the groups. We didn't really have a concern that maybe we were going to see that there would be some benefit that would be restricted to different -- I'm not sure exactly what you're trying to get at.

DR. DUNN: I guess if all the benefit we're seeing is really being driven by an antidepressant effect, we can't answer that question now.

DR. FARCHIONE: Yes, we can't.

DR. DUNN: But how much of a concern, based off of a label that they're potentially trying to get that this is a treatment for PTSD rather than, really, the mechanism that we're seeing across some of these studies is that this is an antidepressant effect, and then kind of associated, we're seeing improvement of the PTSD?

DR. FARCHIONE: But if the primary endpoint is a PTSD measure, that's what we have to answer,

is it improving the PTSD symptoms? So if there are ancillary benefits, great; if there's not, it doesn't really matter. But if it improves the PTSD, that's what's being measured, what's being evaluated, and what we would ultimately be able to label, if we get to that point.

DR. DUNN: Maybe another way to ask this question, if they had not excluded MDE or MDD, and you saw similar outcomes, would that change your enthusiasm about, or I guess consideration of a PTSD limited or exclusive label?

DR. MANTUA: Valentina Mantua, Associate Director of Neuroscience. We had asked that criterion just to avoid that discussion and having confoundings. And whether that criterion is optimal, maybe not; maybe you're right. But this is psychiatry, so there are a lot of dimensions that overlap. So we can't just artificially narrow the population either. So we thought that this was reasonably acceptable.

DR. DUNN: Thank you.

DR. NARENDRAN: Any further questions for

the agency?

(No response.)

DR. NARENDRAN: If not, we can break for lunch. We will reconvene again in the room at 1:30 pm Eastern Time. Please take any personal belongings you may want to with you at this time.

Panel members, please remember there should be no discussion of the meeting topic during the lunch break amongst yourselves or with any member of the audience. Additionally, you should plan to return around 1:20 to ensure you're seated before we reconvene at 1:30. Thank you.

(Whereupon, at 12:33 p.m., a lunch recess was taken, and meeting resumed at 1:30 p.m.)

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

(1:30 p.m.)

Open Public Hearing

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

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

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

Likewise, FDA encourages you, at the

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

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

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only

when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please state your name and any organization you are representing, for the record. You have four minutes.

MR. LYNCH: Good afternoon. My name is Todd Lynch. Thank you for allowing me to speak today. Before I begin, I do wish to disclose that I previously served as a reimbursed consultant for Lundbeck Pharmaceuticals Patient Advocacy Group; however, my appearance today is entirely on my own behalf, and I am not receiving any compensation.

I am 43, married, a father of six wonderful children, three of whom are adults. My perspective is informed by over two decades of lived experience with mental health and substance use challenges, including PTSD and CPTSD. I am now proudly in my fourth year of sustained recovery.

My three adult children, a firefighter/EMT and two actively deployed U.S. Armed Forces personnel, expands my already distinctive perspective. They grew up witnessing the effects

of PTSD firsthand on their parents, both of whom are first responders, and now face similar trauma exposure in their careers. For more than two decades, individuals with PTSD have been in need of additional treatment options. It is my hope that such options will be readily available for my children should they ever be needed.

I also bring the perspective of a mental health professional. I hold a master's and bachelor's in counseling and am a Georgia credentialed Certified Peer Specialist or CPS. My CPS work includes direct care, notably with Georgia's 2024 Pilot-Assisted Outpatient Treatment program. I also served for over a decade as a first responder and 911 dispatcher training crisis intervention. This diverse background provides a unique perspective on this topic.

PTSD is not just anxiety or bad memories; it is a cage. It forces intense avoidance, shrinking your world, and sometimes trapping you at home for weeks. It is a constant exhausting turmoil. One client described it to me as graphic, intrusive,

unblockable pop-up ads for a horror movie based on a true story. This shows how sufferers remain in perpetual fight or flight.

For many with PTSD, first-line treatments such as sertraline are simply not enough. Up to 40 percent of PTSD patients, civilians and veterans, don't respond to current treatments. A study focusing on veterans found sertraline to be no more effective than a placebo for many. This highlights the harsh reality of PTSD, especially after two decades with no new medication options.

That makes this new data on adjunctive brexpiprazole profoundly important, as it shows a statistically significant reduction in overall PTSD symptoms. This goes beyond just the total score of the CAPS-5 scale. The evidence showed improvement across all four of the core clusters of suffering: the intrusive memories which hijack the present; the avoidance which isolates us; the negative beliefs that steal our hope; and the hyperarousal that denies us a moment's peace. This offers a new scientifically validated path, which could result

in a shift for many from barely surviving to truly thriving.

I understand the serious risks linked to this type of medication, which always must be a major consideration in any treatment plan. All treatment decisions should be made with a licensed professional's direct supervision and close consultation; however, as both a patient and a professional, I am aware that severe untreated PTSD can by itself be life threatening on a daily basis.

The recent and pivotal trial demonstrates that combining brexpiprazole with sertraline marks a significant advancement in treatment. This combination exhibited enhanced tolerability compared to sertraline monotherapy, resulting in fewer discontinuations due to adverse effects. These findings suggest that this injunctive treatment has the potential to effectively alleviate PTSD symptoms and support recovery.

Please, give our clinicians and our patients, both current and future, another tool. Review the data, as well as the lived experience

that data represents and, please, recommend approval of this request. Thank you for your attention, your time, and for your service on this vital committee.

DR. NARENDRAN: Thank you.

Speaker number 2, please state your name and any organization you are representing, for the record.

MR. WINTON: Good afternoon. My name is Jeff Winton, and I am the Founder and Chairman of Rural Minds. Rural Minds is the only national 501(c)(3) non-profit patient organization dedicated to advocating for rural mental health equity and addressing the stigma surrounding mental illness for the 46 million people living in rural America. The work that we do is funded by individual donors and companies, including the sponsor. I am also a dairy farmer and the uncle of a young farmer who died by suicide near our family farm in Upstate New York.

Diagnosing and treating post-traumatic stress disorder is a significant concern for our

organization. Military veterans, for example, make up approximately 10 percent of the rural population; yet, while rural areas only make up 14 percent of the total U.S. population, they contain nearly a quarter of all veterans. In other words, veterans are overrepresented in rural communities compared to the general population.

We understand that the difference in PTSD between veterans and civilians may seem small, but veterans seeking care actually show much higher rates of PTSD. Recent combat veterans face significantly elevated risks. This indicates that military service, particularly combat exposure, may substantially increase PTSD risk. The truth is that any American in a rural setting already faces incredible challenges in receiving treatment for PTSD and other mental health issues.

Our access to care is a huge stumbling block. Rural areas often lack sufficient mental health professionals, specialized trauma centers, and resources like telehealth services, making it difficult for individuals to access timely and

appropriate care. Long distance to healthcare facilities and limited transportation options exacerbate the challenges of accessing mental health services in rural communities.

Add to that the stigma surrounding mental illness, particularly PTSD, that is often more pronounced in rural communities because of the close-knit social structures and cultural norms that emphasize self-reliance and independence. With this very challenging treatment environment, the approval of a therapeutic like this one we are discussing today for PTSD is important to rural communities.

A small molecule of medicine is vital for mental illness, as it can reach the brain more easily. The availability of the medicine as a pill alleviates the additional complication of veterans having to access a physician for treatment. In rural areas, there are fewer healthcare providers, and they tend to be much further away from where we live. Since rural areas have no public transportation, this is particularly a challenge.

We strongly support the approval of this medicine for the treatment of PTSD. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 3, please state your name and organization, for the record.

MR. BLAKE: I am Ron Blake. Folks call me Blake. The sponsor is reimbursing me for my travel here from Phoenix, Arizona. I am not receiving compensation. I'm representing myself with my story.

Three men entered my Phoenix, Arizona home while I was asleep just days before Christmas one night. I was held down, beaten, and raped, being significantly injured and eventually diagnosed with PTSD. I've been advocating for a lot of others on my ongoing 10-year, cross-country journey to recover from PTSD and to reach a symbolic goal involving a popular late night comedy show.

I gave a TEDx talk about how a fortuitous moment of laughter from The Late Show with Stephen Colbert stopped me from dying by suicide at 10:44 pm on November 2, 2015. That spark of hope

sent me out on this now 97,000-mile hero's journey to learn how to re-engage with society after I had isolated so badly. I had to learn how to face my fears, learn how to process the trauma, and I've been getting support from my efforts to get to my symbolic goal to become a guest on The Late Show with Stephen Colbert.

Along the way, I've engaged 34,453 complete strangers, one by one. They've all opened up to me about how they've been impacted by PTSD. Those folks have shared powerful stories of support for my determined efforts. There are 94 languages with 32 Sharpie marker colors, and they're on 519 giant foam boards. It's a massive collective story of struggles; isolation; heartbreak; loneliness; tragedy; and nightmares. But it's a lot more than that, too, you guys. It's also an incredible collective story of moxie; optimism; ingenuity; discovery; exhilaration; triumph; and some laughter along the way.

I've received abundant medical services for surgery and extensive physical therapy that I've

needed following the trauma. A violent crime victim compensation program through the local prosecutor's office in Arizona, they've assisted me. They've been providing me with funding to restore some financial stability after I sustained $110,000 in financial trauma losses, but it's the PTSD part of my overall recovery that's been the most challenging for me. A team of counselors and psychiatrists have worked with me over the years. I've had a lot of successes, you guys, and I've come a long way; however, the recovery continues to be a work in progress.

Somehow I also survived a suicide attempt back in May of 2015, but many people I've met on my travels -- from Washington Square Park in Manhattan, to Coe Library at the University of Wyoming, to Swami's Beach in Encinitas, California, and a lot of places in between -- those people have opened up to me about their own suicide attempts. Scores of other folks shared stories of those we lost to suicide. We know it. PTSD is formidable. All of those individuals hold out hope for the same

thing I do, for additional treatments and viable options like the treatment you're reviewing today to help us move beyond the debilitating injurious impacts of PTSD.

Lastly, I wanted to say, after this open hearing is done, if any of you guys want to read some of the stories of support that people all over this country have been putting -- these are the small boards I brought in from Phoenix. I can't carry the large ones on the airplane. But if you want to read some of these -- and you can also add a story of support, if you want, I have some extra boards -- for my efforts to continue recovering from PTSD. I've spent now 24,000 hours of my life to get on as a guest on The Late Show with Stephen Colbert. Do not give up on me, you guys. Somehow, some way -- it is very symbolic for me -- I'm going to get on that show in the next 10 months before it's canceled.

(Laughter.)

MR. BLAKE: Thank you. Thank you, guys.

DR. NARENDRAN: Thank you.

Speaker number 4, please state your name and organization, for the record.

DR. ABRAMS: Yes. Good afternoon. I'm Dr. Michael Abrams, a health researcher with the consumer advocacy organization, Public Citizen. I have no financial conflicts on the matter today.

The PDAC is considering the approval of the antipsychotic and antidepressant drug combination of brexpiprazole and sertraline for the treatment of post-traumatic stress disorder. The drugs are approved as, as we've heard, as individual pharmacotherapies for the treatment of psychotic, depressive, and anxiety disorders.

Brexpiprazole was recently approved for the controversial indication of agitation in older adults suffering from dementia despite a boxed warning that such use heightens a patient's risk of premature death. Sertraline has long been approved as a monotherapy for PTSD, although it typically results in the desired response to treatment of only about 32 to 67 percent.

Notably, the supplemental application of

brex and sert seeks an approval of this combination as an initial therapy for PTSD, not used as an adjuvant to an SSRI treatment that fails to sufficiently address PTSD symptoms, as would typically be the case.

The evidence to support the supplemental application we're hearing about today is data from three randomized clinical trials. FDA's scientific review of these studies was quite straightforward. One phase 3 trial was robustly positive. The other phase 3 trial was, quote, "clearly and convincingly negative."

To address these conflicting results, the sponsor performed additional analysis of data from an older phase 2 trial. The two phase 3 trials were similar in participation, and composition, and study design, with 321 participants. The first study observed a 10-week improvement in DSM clinician-derived PTSD scores, averaging about 6 points in persons taking the brex-sert combination compared to a placebo-sert combination. The second study, 416 participants did not show a

significant benefit from brex-sert treatment.

To salvage the application, it seems the sponsor reached backward in time to a third study which randomized 516 participants into four treatment groups based on different dose combinations, including a full placebo regimen. That study found that after 10 weeks, the brex-sert combination performed an average of 5 points better on the PTSD score than placebo and sertraline together. This result, however, was only nominally significant and reliant certainly on post hoc comparisons that were not prespecified, and thus the analyses should be regarded as biased.

Finally, it should be noted that across all nine treatment arms spanning the three clinical trials, participants improved markedly regardless of the treatment used. This included a 10-point improvement in a group who received placebo only; 10 points being important, of course, because that's FDA's and others' criteria for a clinically meaningful improvement.

Accordingly, the evidence supporting the use

of combination brex-sert as a treatment for PTSD is weak, at best, based on two conflicting phase 3 trials and a questionable post hoc analysis of data from a phase 2 trial. Moreover, the sponsor acknowledges that brex-sert combination has the many and sometimes serious adverse effects of each drug individually.

In sum, the evidence presented should be used by this advisory committee, we believe, and by the FDA to reject this combination of brex and sert as a treatment for PTSD. Superiority over mono, serial therapy, or even placebo therapy has simply not been established. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 5, please state your name and organization, for the record.

MR. CHRISTY: Thanks for letting me speak. My name is John Christy. I live in Oakland, California, and I'm a retired San Francisco Fire Department firefighter/paramedic. I retired in 2018 with 36 and a half years of active duty service, having worked as a paramedic, rescue, EMS

captain, and firefighter paramedic, and 30 of those years were spent in the field.

I also led the San Francisco Fire Department Peer Support Team for 6 and a half years. The San Francisco Fire Department has a dedicated peer support team that consists of two full-time active duty firefighters who help department members navigate the toughest calls. This includes professional support for our post-traumatic stress injuries, PTSD, and support of their families.

I'm not being compensated in any way for my testimony today. My relationship with Otsuka is as a consultant on the subject of trauma from the perspective of a first responder and someone who's healed from PTSD, and I was also interviewed for a training video related to PTSD. I've helped hundreds of people navigate emotional trauma, and their families, first as a peer counselor, and now I work as an executive coach with high-stake leaders.

In 2008, I called the peer support team for help and was referred to a trauma counselor for

what was called severe PTSD and high risk of suicide. Over several years, as I healed, I came to understand that much of my experience was related to the lack of support for PTSD, in general, and the mindset of PTSD being seen as a weakness instead of what many experts now describe as a physiological and psychological injury with long-term changes in neural circuits and the stress response.

It's also not always one big incident. As in my case, sometimes it's accumulation of hundreds of calls, thousands of small moments, the ones you're expected to forget and the ones nobody asks you about. It builds in silence and isolation, and then being told directly or indirectly that what you're feeling doesn't matter.

I appreciate the need to be cautious concerning the use of pharmaceuticals with PTSD, and I'll leave the actual risk analysis to those more qualified. But I want to say this as a career first responder and as a person who's healed from PTSD. This is a serious situation and requires us

to think outside the box and explore new ideas. A house is on fire. We have an emergency situation in the first responder community alone.

I just recently looked up some data. Since I retired in 2018, the total number of first responder suicides, reported suicides, is over 1,400, and department heads and advocacy organizations continue to report a rise in mental health crisis across professions, and those are 1400 families, either their mother or father, son, daughter.

As a paramedic who's been involved in emergency situations, I can confidently say that my ability to think outside the box has saved hundreds of people. So I say, we need to ask ourselves, "Am I doing all that I can to help those that are dealing with PTSD?" And I say that from a place of strength. Thank you for letting me speak.

DR. NARENDRAN: Thank you.

Speaker number 6, please state your name and organization, for the record.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman,

President of the National Center for Health Research. Thanks so much for the opportunity to speak today. Our non-profit think-tank analyzes and scrutinizes research, focusing on the safety and effectiveness of medical products, and we do not accept funding from any entities that have a financial interest in our work, so I have no conflicts of interest.

My perspective is as a scientist trained in psychiatric and psychosocial epidemiology at Yale Med School, and I previously held research positions at Yale and Harvard, and moved here to work in the U.S. Congress, HHS, and the White House before my current position.

PTSD is a terrible condition, as you've heard, and there are numerous treatments, some more effective than others. Veterans have told me that medications often create problems that are worse than what they're trying to solve, so any treatment should be based on very clear evidence that its benefits outweigh the risks. This meeting is very important, and I thank you for your service.

The company designed two adequate and well-controlled studies, and Study 071 showed a benefit, as you know, but Study 072 did not. Now, FDA sometimes approves drugs based on just one study, but the problem here is that the second study had the opposite results to the first study, and it shows no benefit with a non-significant level of p is greater than 90. For those unsure about p-values, that means there's a 90 percent chance that the drug combination was not beneficial in that second study, so the sponsor wants us to think about Study 061 instead, which was an exploratory study.

We agree with the FDA that Study 061 did not appropriately control for the numerous statistical comparisons, and the sponsor's evidence is also based on several post hoc analyses, and those are not kosher from a scientific perspective. And, of course, Study 061 is even less persuasive because the larger, better designed Study 072 did not show any benefit or even a hint of a benefit.

So what about the risks? The serious risks

of these drugs are well established. We should especially be concerned about the risk of suicidal thoughts and behavior for youth and young adults for each of these drugs because, number one, many veterans and abuse patients with PTSD are teenagers or young adults.

Number two, PTSD patients and veterans are already at high risk of suicide, as you know, and I've spoken with veterans groups that have stated that the use of multiple psychotropic drugs concurrently are contributing to very serious mental health problems, with rebounding when patients try to reduce their risk. In contrast to what we've heard, these combinations are often not well tolerated.

Number three, PTSD patients often self-medicate with alcohol and other drugs, in addition to their prescription drugs, so FDA should be even more cautious when considering this combination for approval. There are other serious risks as well, and let me just say that weight gain, metabolic disorders, and suicidal thoughts,

and other side effects could become more obvious in the months after these 12-week studies were completed and could be greater when they're given in combination.

So in conclusion, the FDA previously approved these drugs despite the risks because the agency determined that the evidence of benefits for patients with schizophrenia, depression, and other indications outweigh the risks. But in your review today, there is not clear evidence that there is any benefit for PTSD, and for that reason, it seems impossible to conclude that the unproven benefits of these combined drugs for PTSD outweigh the well-established risks. And keep in mind that monitoring for these side effects in the real world is likely to be much less effective than in clinical trials, and particularly in rural areas. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 7, please state your name and organization, for the record.

(No response.)

DR. NARENDRAN: You're muted.

MS. WITCZAK: Are you able to hear me?

DR. NARENDRAN: Yes, we can hear you now.

MS. WITCZAK: Okay.

Good afternoon. My name is Kim Witczak. It feels strange to be on this side of the table after spending nine years as the consumer representative on this very committee. I served three consecutive terms. I'm a long-time drug safety advocate and co-founder of Woodymatters, started after the sudden death of my husband just weeks after being prescribed Zoloft for insomnia. Since then, I've spent two decades pushing for transparency, accountability, and stronger protections for the unsuspecting public.

I'm here today because this application deeply concerns me. For starters, let's look at the efficacy. Phase 3 data are inconsistent at best. Study 071 shows a modest statistical benefit, just a 5-6 point improvement on the CAPS-5 scale, but 072, equally powered, failed to meet both its primary and secondary endpoints. So to

make up for the failure, the sponsor leans on study number 061, an exploratory phase 2 trial never designed to confirm efficacy.

They abandoned their prespecified statistical plan after the study ended. They ran multiple post hoc comparisons and applied three different multiplicity corrections to extract significance. Even the FDA reviewers flagged this as potentially overinflating results.

This isn't solid science. In my opinion, this is statistical gymnastics. Even if one study reached statistical significance, what does that actually mean, it works in the real world? These trials excluded patients with suicidality, anxiety, substance abuse, and common medical conditions, the very people who most likely are going to receive this combo in clinical practice. So yes, it may look like it worked on paper, but in a narrow, ideal, and sanitized population. But that's not generalizable, and that's not meaningful.

And while this committee is tasked with reviewing efficacy, we cannot overlook the most

important issue here, which is safety. This application proposes starting two powerful psychiatric drugs simultaneously on day 1. Individually, they each carry serious risks, and yet there's no single long-term study on the combination. PTSD is a chronic condition, but these trials only lasted 12 weeks and no data on what happens six months, a year, or longer.

Rexulti is associated with akathisia, weight gain, sedation, and we know Zoloft carries a black box warning for suicidality, emotional numbing, and sexual dysfunction. Both drugs have severe withdrawal profiles, yet no data is provided on how to safely stop or taper. Once again, the burden of risk will fall on patients, not this committee, not the prescribing doctors, or the companies profiting from the prescriptions.

We've seen this movie before. A drug gets approved based on narrow trials marketed aggressively, and then the real harm unfolds in the real world after it's too late. But let's be honest about what's really happening here. Zoloft

is already approved for PTSD, and now it's generic. The sponsor doesn't profit from sertraline; they profit from Rexulti, a high-priced, branded antipsychotic still under patent. This is a market expansion strategy, not a medical breakthrough. It's securing a new indication for Rexulti, which extends their patent while riding the marketing wave of being touted as the first new PTS treatment in two decades.

Hope without strong, reliable data is dangerous, especially for the population as vulnerable as those with PTSD. You can't put the genie back in the bottle. These stakes are high. PTSD patients, especially our veterans, deserve real solutions, not a marketing strategy wrapped and recycled, and manipulated science, and sold as new. So please reject this application. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 8, please state your name and organization, for the record.

MR. SABO: Good afternoon, chairperson and

distinguished members of the advisory committee. My name is Clark Sabo. I'm a retired Marine Corps veteran from Cincinnati, Ohio, and I'm here today to share my lived experience with post-traumatic stress disorder. For full transparency, I want to disclose that my travel and related expenses were covered by Otsuka. Thank you for giving me the opportunity to speak and for your dedication to hearing the voices of veterans and patients as you weigh these important decisions.

When I joined the military, everyone was told they have a bullet with their name on it. We all hope to never find that bullet. After being medically retired from the Marine Corps in 2012, I thought I left that fear behind me, but in 2020, I was diagnosed with PTSD, and suddenly a relentless wave of emotions crashed over me. I started having panic attacks at the grocery store. I couldn't visit the restaurants I used to love. No place felt safe anymore, not even my own couch. The reality hit me that the bullet with my name on it is the one in my chamber.

My weapon was loaded for me during boot camp. My PTSD comes from a source many people never consider. I was sexually assaulted in boot camp. That trauma left deep scars on my mind that I've been trying to heal ever since. Over the years, I've been prescribed more than 15 different medications to manage my PTSD symptoms, not to mention ketamine infusions, medical marijuana, eTMS and multiple rounds of inpatient and outpatient therapy. Each new medication felt like a game of Russian roulette, often prescribed alongside others, sometimes without full consideration of their combined effects.

I want to acknowledge that many traditional medications have helped men and women living with PTSD, and I respect their journey, but I'm here today for my brothers and sisters who die by suicide every 11 minutes in this country. In the next hour, 6 veterans and service members will die.

We often talk about honoring the sacrifices of our veterans, but I can't think of a better way than by expanding treatment options by offering

just one more glimmer of hope. Sometimes, one small pill can be the reason someone chooses to keep fighting. According to the Department of Veteran Affairs, an estimated 15 to 30 percent of veterans experience PTSD at some point in their lives, and it's not just about combat. Many, like me, develop PTSD from non-combat trauma, military sexual assaults, accidents, and other service-related experiences. In fact, about 1 in 10 veterans with PTSD develop it from non-combat trauma.

PTSD is a complex, deeply personal struggle that cuts across all backgrounds. For years, like so many others, I have lived under a shadow, constantly reminded that tomorrow isn't guaranteed, that my son could lose his father, and my wife could lose her husband. I fight every day, silently suffering with invisible wounds that grow deeper and deeper with each failed treatment. Otsuka's new medication, brexpiprazole in combination with sertraline, could be the life-saving treatment that disarms my weapon and

puts the safety on.

For me and countless veterans and Americans, it could finally mean stepping out of the shadows and seeing the beauty of the country we proudly served. I urge the committee to consider the profound impact of expanding the treatment choices we can have, not just on symptoms, but on lives saved. The millions of Americans living with PTSD and the families who love them deserve this innovation. Please help us turn the tide on this silent epidemic, and give me and everyone suffering from PTSD one more chance at life. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 9, please state your name and organization, for the record.

DR. MAASS-ROBINSON: Good afternoon. I am Saundra Maass-Robinson, a physician and board certified psychiatrist with over 35 years of experience in both clinical practice and research focused on mental health. I want to state that I have no personal financial interest related to our discussion here today, nor am I being compensated

for my time.

I am presenting here at the request of Otsuka Pharmaceuticals, as my recent work has involved leading clinical trials aimed at discovering more effective treatments for post-traumatic stress disorder, specifically looking at the combination of brexpiprazole and sertraline.

The impact of PTSD has been well described here, so I would like to describe this condition as a serious and often life-altering experience that can develop after someone experiences or witnesses a traumatic event. It's well associated with combat, but also following physical or sexual assault, natural disasters, and even personal accidents. The symptoms of PTSD are varied, and they can include these intrusive flashbacks, nightmares, emotional numbness, hypervigilance, and a tendency to avoid situations that remind the individual of the trauma; and many people, as described here, also find themselves feeling isolated and disconnected from their loved ones.

The human toll of PTSD is staggering. It not only affects emotional well-being, but can also take a significant toll on physical health. Relationships suffer, careers can be derailed, and the overall quality of life diminishes drastically. And in addition, there's a well-established association between PTSD and an increased risk of dying by suicide.

Unfortunately, this condition is often misunderstood, it's underdiagnosed, and it's definitely inadequately treated. In my experience, patients have come to me with a history of being treated based upon their presenting symptoms to a previous provider. This leads to a cycle of ineffective treatments and multiple medications that only address the symptoms rather than the root cause. The outcome of that has been well described as well.

And while there are effective treatments available for this condition, access to these options is often limited by financial constraints; and moreover, not every treatment works for every

individual, and side effects are variable as well with medications and their combinations. In psychiatry, it's common to combine medications to enhance their effectiveness, as many have complementary effects; however, as in all fields of medicine, management of treatment requires management of side effects. This highlights the importance of ongoing research and drug development to better understand how different treatments can work together and effectively.

As the principal investigator in recent clinical trials, I explored the combination of brexpiprazole and sertraline for treating PTSD using established clinical scales to measure changes in symptoms, illness severity, and quality of life over this 12-week period. The combination of brexpiprazole at doses of 1 to 3 milligrams per day with sertraline showed clinically meaningful improvements compared to a placebo group. There were not significant adverse events, and there were no drug-related fatalities. Since both medications have been on the market for other indications,

their approval in this combination could offer potentially affordable treatment for many individuals suffering from PTSD.

Thank you for the opportunity to share this important information with you today, and together, hopefully we can work towards a better understanding in treating this condition, and certainly improving the lives of those who are directly affected by it.

DR. NARENDRAN: Thank you.

Speaker number 10, please state your name and organization, for the record.

MS. PLOTNICK: Good afternoon. I'm Debbie Plotnick, and I am the Executive Vice President for State and Federal Advocacy at Mental Health America. Thank you for the opportunity to be here. At MHA, we have more than 140 affiliates in 42 states, and it's been my privilege to serve at MHA for almost 20 years. MHA was founded in 1909, and for all of its 116-year history has been the voice of people living with mental health conditions.

When we think about PTSD and the approximately 30 million Americans who are diagnosed in any given year, veterans most often come to mind. Veterans' experiences are what most often are represented in the public discourse, but veterans are only one group of people affected by PTSD. Seven out of 10 veterans will have PTSD in their lifetimes, but as many as six out of 100 members of the general public, which is a much, much larger group, will also experience PTSD.

PTSD, as you've heard, causes real suffering. People's symptoms include, but are not limited to, chronic pain; sleep disturbances; feeling on edge; angry, aggressive outbursts; suicidal ideation; and suicidal attempts. PTSD is highly correlated with suicide attempts and completed suicides.

We know that the etiology is pretty complicated, but it usually has to do with injury, an injury that causes PTSD, or sometimes sudden. We've heard about some of them such as traumatic accident or other kinds of adverse incidents.

Sometimes they occur, though, over time, much like a stress fracture. This can be due to living in a long-term stressful environment such as domestic violence or having experienced a traumatic childhood.

Other long-term stressors that result in PTSD include living with a chronic illness, facing systemic discrimination, bullying, or living in communities where violence is endemic. It might also include discrimination associated with living with a mental health condition or a substance use disorder. It's estimated that over half those affected by PTSD do not seek a formal diagnosis due to stigma, previous ineffective treatment, or because of barriers accessing healthcare, especially mental healthcare.

Over the decades, we at Mental Health America and our national affiliates have listened to countless powerful stories told by those experiencing PTSD. Since 2014, Mental Health America has offered free, anonymous, clinically validated mental health assessments to the general

public and has captured over 25 million screens for conditions like depression, anxiety, and, of course, PTSD. People tell us about their pain and that they want safe and efficacious treatments.

When PTSD is recognized and treatment is offered, it often is involving one of the two clinically approved, FDA-approved PTSD treatments, and that has been not helpful for many, many people, as you've heard today. Because of the dearth of treatment options, combined with the fact that people have been tried and been failed by existing medications and existing approved treatments, the sufferers often try to alleviate their pain themselves with misuse of alcohol or opioids. Some even seek substances that are presently available only outside of the country or through unregulated or illegal and unsafe means.

As the nation's oldest advocacy organization, MHA fights to bring awareness about mental health needs and access, and treatment and support, to people who want to alleviate their mental distress. It's essential that the FDA

facilitates new medication options for PTSD as one of its highest priorities. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 11, if you want to state your name and organization, for the record.

DR. SAUVE: Good afternoon. I'm Dr. Will Sauve. I'm the Chief Medical Officer at Osmind. I'm a psychiatrist and Navy veteran, and I have no other financial relationships with any part of industry.

I was trained right down the road at the Uniformed Services University of the Health Sciences, and then completed by psychiatry residency at the National Capital Consortium in 2004. What that means is that I watched the smoke rise from the Pentagon in 2001 from the 5th floor of Walter Reed, which was the inpatient psychiatric unit at the time. I spent the next 2-3 years taking care of casualties in that setting coming home from the war.

Upon graduation in 2004, I immediately joined the 7th Marine Regiment in the Al Anbar

Province in Iraq, where I spent about two years in combat with my unit. After that, I returned to inpatient psychiatric work at the Naval Medical Center in San Diego for five years; and when I separated from the Navy after that, I went to Virginia to run an inpatient PTSD program for three years.

The reason for that introduction is meant to get across why I have the nerve to be honored to talk to this committee about PTSD today. So that was the point of that dramatic interlude.

The scope of PTSD in the United States, approximately 5 to 6 percent suffer PTSD in a given year, which translates to as many as 13 million Americans per year with a diagnosis of PTSD. In the veteran population, the incidence is about the same in the overall population, but when you look at the OIF-OAF population specifically, it's actually as high as 15 percent, and the estimated annual cost to the country is nearly a quarter trillion dollars. That includes healthcare costs; disability; lost productivity; chronic illness;

premature mortality; and more.

As far as current resources and tools, the approved treatments in the United States' number is 4. Of the two medications approved, sertraline was approved for PTSD in 1999; paroxetine was approved in 2001. There have been no new medication treatments approved for over two decades.

Then on to the question at hand, sertraline plus brexpiprazole, the medication being considered today, comprises two already approved medications for other indications: sertraline in common use for more than 30 years, brexpiprazole for 10. As brexpiprazole is approved for adjunctive use and depression already, it is commonly combined with most of the antidepressant class drugs for MDD and, by coincidence, with PTSD as well, as these conditions are quite frequently diagnosed together.

You've all seen the phase 3 data published recently, which indicates a clinically significant improvement in the group taking sertraline plus placebo, let alone an even greater yield when you combine sertraline plus brexpiprazole, with the

adverse events being quite small.

So, in summary, PTSD currently affects 6 percent of all Americans with the available tools for treatment being quite limited at this time. No new medication treatments have been approved in over 20 years. Sertraline and brexpiprazole are already in common use, both separately and in combination for 10 years already, and the two in combination for PTSD can yield nearly 50 percent symptomatic improvement versus about a 35 percent improvement with sertraline alone. Thanks for the time.

DR. NARENDRAN: Thank you.

Speaker number 12, please state your name and organization, for the record.

DR. KNUTSON: Hello. My name is Dr. James Knutson. I'm a board certified psychiatrist and a principal investigator for Core Clinical Research in Everett, Washington, which is about 30 miles north of Seattle. I have no financial interest, and I've not been paid in any way to participate today. I can only say that three weeks ago, this

sounded like a great idea, and today, not so much, but I'm here and happy to testify.

We were involved with all three of the Otsuka trials for PTSD. We're an independent site, a moderate site of about 12 people or so. My goal in testifying today is basically to present a perspective of an independent site. We had previously participated in a PTSD study of military personnel, or service-connected personnel, about seven years ago. In that study, we also used the CAPS-5, and many of the subjects that participated in that study had serious difficulty in completing the CAPS. One patient even became angry and walked out of the assessment. I think we forget the impact of some of these assessments on the subjects that we're trying to extrap data from.

We had similar experiences with almost every patient, or every subject, in that study. The reason I'm bringing this up is because, for the military-connected subjects, they across the board told us that they would not reveal their symptoms while they were connected to the military, to their

wife, their best friend, their family, or anybody else, for fear of losing their security clearance and losing any chance of job promotion.

The other main issue for them was they did not want to be known to the VA. We began these studies pre-COVID, and what was interesting is that we had multiple folks that called in while we were pre-screening who wanted to use COVID as their index trauma, but they were obviously excluded for that.

I'm here mainly to talk a little bit about the fact that we haven't had any effective PTSD medication approvals since 2001. I also founded a detox and residential treatment facility at the height of the opioid crisis, and the number of folks who come in for detox who also have PTSD is very high. At our facility, it is as much as 50 percent or higher. The problem is that we can treat their alcohol and drug disorder, their substance use disorder, but if their PTSD is left untreated, they remain at serious risk for relapse. And the available treatments for PTSD in Spokane,

which is where the facility is located, Spokane, Washington, is limited, at best, or practically non-existent.

I also wanted to mention that some of the responders that we had in this study had significant improvements in their symptoms, including going from a rating of 3, which is severe, down to 0, mild or non-existent.

DR. NARENDRAN: Speaker number 12, you may want to wrap up.

DR. KNUTSON: Okay. I just would like to urge the committee to approve this medication treatment. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 13, please state your name and organization, for the record.

MS. WALKER: Good afternoon. My name is Vanessa Walker. I am here on behalf of DBSA, which is the Depression and Bipolar Support Alliance. I live here in Washington, DC, but I am a consultant for DBSA. I work with them on advocacy and engagement, but I'm also here as someone with lived

expertise when it comes to PTSD.

I wanted to start by acknowledging that DBSA is treatment agnostic when it comes to events like this. We believe that we need to have many, many tools to treat individuals with conditions such as PTSD. Every individual is different and every individual needs a treatment that is unique to them. DBSA also believes strongly in the combination of medical treatment, medication, as well as peer support. I wanted to mention that because we have talked a lot about peer support here today.

For me, about 10 years ago, if someone had said to me, "Do you have PTSD?" I would have said, "No. I never went to war. I've never experienced a violent sexual trauma." But what I have experienced is abandonment. I was abandoned as a child. I was diagnosed with breast cancer at a very young age for the first time at 30, for the second time at 36. I did experience emotional abuse in my first marriage, as well as some sexual abuse that was emotionally related. And my PTSD

came on slowly, and I did not want anyone to label me with another condition.

So one of the reasons I am here today is because, as we've heard from other speakers today, PTSD is a condition that is not just limited to people who have been in combat. It affects people like me. It affects people like my mom. It affects people like my neighbor. It affects many, many people. And the stigma that is attached to a diagnosis like this is great. I have been told that I should stop talking about my mental health conditions because it might limit my opportunities when it comes to the workforce. I'm currently getting my MPH at UNC because I realized that I needed to have even more information so that I could fight the stigma that was out there.

So today, I'm here not to say yes or no to that which you are making a decision on, but what I am here is to say that we need as many tools as possible. We need as many tools as possible in the toolbox. People need help, and we have the opportunity to create treatment plans that can help

individuals. And if this is one of them, then we should explore that. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 14, please state your name and organization, for the record.

MR. BRIGGERY: Yes. My name is Lloyd Briggery, and I'm not representing any organization. I'm a U.S. Army combat veteran. I was a tanker. I spent two and a half years deployed to Iraq, fighting. The last year and a half, I was in Ramadi. And if you don't know where Ramadi is, it's the city they make all the Hollywood movies in reference to the Iraq war about.

I spent the first 10 years of my life -- of my adult life, we'll say -- in the Army, from the age of 17 to 27. What I never was taught was how to turn off the rage of war upon my return to civilian life. In fact, I wouldn't be diagnosed with PTSD until nearly three years after I got out.

My first six months out of the military, I decided to move to New York City, and I found

myself very drunk wandering the streets of New York. And I stumbled into what I thought was a nightclub but was actually a very palatial lobby of a church in downtown Brooklyn. Shout out to Brooklyn Tabernacle. It turns out this church had a recovery group that was led by a licensed therapist who just so happened to be a Vietnam veteran, and so my journey to healing began.

Over the years, he and I established four pillars that empowered me to rebuild my new life, and these pillars were purpose, impact, community, and fitness. With purpose, I discovered a new dignity and a new mission in life. With impact, it was finding significance in this new mission, and as a result a new identity with community, having a new mindset, and then surrounding myself with like-minded individuals to work together for a new cause.

With fitness, this is the most recent discovery. Recent studies have shown that the norepinephrine system, the fight or flight stress reward system that we have, is disrupted by PTSD.

It turns out short, intense workouts help to regulate the system, and they teach my body how to come back to baseline. This is a real-world transfer in resetting my body's stress response. And here I thought this entire time I was just a gym bro. It turns out these workouts are and have been essential to my healing.

During the screening of my diagnosis for PTSD, I was told by the assessor at the VA to just stop talking. He was visibly disturbed by my answers, and I hadn't even gotten to the good stuff yet. Please do not pity the soldier, the warrior, for fighting in the war. Given the opportunity, most of us wouldn't hesitate to fight again. The great trauma was in not having the tools to manage ourselves after the battle.

My journey to healing has been a daily ongoing process for the past 17 years. It's been, by the grace of God, lots of therapy and a good amount of trial and error. In fact, this fourth pillar, pillar of fitness, is something that I recently learned this year. I'm grateful for my

journey, but with new pharmacology and therapeutic procedures, I could have shaved years off this process, and time is the one resource that we can't get back. I believe a full, comprehensive approach on all levels will streamline this healing process. Thanks for your time.

DR. NARENDRAN: Thank you.

Speaker number 15, please state your name and organization, for the record.

MS. SANTORO: Good afternoon. I'm Kathryn Santoro. I'm speaking today, representing the Policy Center for Maternal Mental Health. I'm not being compensated for my remarks today, but various companies, including the sponsor, have sponsored our organization's annual conference.

The Policy Center for Maternal Mental Health is a non-profit organization working to solve challenges in diagnosing and treating those with maternal mental health disorders in the United States. While PTSD has often been associated with veterans and survivors of violence, an underrecognized yet widespread form is

childbirth-related PTSD. Childbirth-related PTSD is characterized by re-experiencing the trauma, hyperarousal, and avoidance behaviors that often interfere with bonding, breastfeeding, sleep, and basic caregiving tasks. Tragically, in some cases, the infant becomes a trigger for the trauma response, worsening isolation and distress for new mothers.

Imaging studies show that individuals with childbirth-related PTSD exhibit heightened activity in the brain's fear center when recalling their birth experience or even hearing their infant cry. Up to 90 percent of those with childbirth-related PTSD also experience postpartum depressive symptoms, and emerging research suggests childbirth-related PTSD may contribute to adverse developmental and behavioral outcomes in children. Between 5 to 20 percent of birthing people experience clinically significant PTSD symptoms, a number that is likely higher due to underreporting.

Childbirth-related PTSD is a serious, distinct maternal mental health disorder with

lasting consequences for both mother and child. The need for effective, safe, and accessible treatment options is urgent. The proposed use of brexpiprazole in combination with sertraline for PTSD, supported by randomized controlled trial data, offers hope to millions of adults with PTSD, including the growing population of mothers experiencing childbirth-related PTSD.

As a national organization committed to improving maternal mental health, we urge the FDA to give full and favorable consideration to this application. The approval would not only offer a new therapeutic tool for clinicians, but could catalyze a shift in recognizing and addressing trauma experienced during childbirth, a form of PTSD that has been too often overlooked. Thank you so much for your time.

Clarifying Questions (continued)

DR. NARENDRAN: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

Before we move to the discussion, I just want to ask if the sponsor wants to respond to some of the questions that were asked?

DR. KRAUS: Yes. There was discussion --

DR. NARENDRAN: And try to limit it to five minutes.

DR. KRAUS: -- with Dr. Dunn, with us, and then subsequently with the FDA, regarding SSRI distribution in the 061 study. We were able to refit the primary model, adding prior SSRI use to the model to address this potential imbalance.

In the prespecified model, the CAPS-5 primary endpoint week-10 effect size was minus 5.08 and the p-value 0.0106. The model with prior SSRI use produced an effect size on the CAPS-5 primary endpoint of minus 5.28 with a p-value of 0.0081. So effect size increased a tiny bit with this, but it seems that the potential imbalance in SSRI use did not drive the result in Study 061.

There was just one other clarification that I did want to make in the discussion before the lunch break. There was reference to variability in

the placebo arm in the phase 3 studies. To clarify, this is the sertraline arm within the phase 3 studies, where we're comparing to an active comparator, not to placebo. And again, similar to what we saw in the registration trials of sertraline, we saw that level of variability. So I just wanted to make sure we clarified that language. Thank you.

DR. NARENDRAN: Dr. Dunn, do you have a question?

DR. DUNN: Yes. Can you explain the model that you did? So you isolated just patients, or subjects, who had prior SSRI use across all four arms in 061, and that's combination versus sertraline result?

DR. SONG: The model is very simple. We just rerun the prior use model and just added this covariate of prior use of SSRI, yes/no. So we just added this covariate, and statistically this could potentially adjust imbalance at a baseline, which was your question.

DR. DUNN: And the difference in CAPS score

that you saw, that is the combination versus search sertraline alone?

DR. SONG: Right.

DR. DUNN: Thank you.

DR. NARENDRAN: Thank you.

I guess we could now move to our panel discussion.

Oh, Dr. Dunn has a follow-up question about another part of the question.

DR. DUNN: Were you able to get the E-TRIP numbers as far as treatment resistance?

DR. KRAUS: The E-TRIP values are individual listings at this point in time, so we were unable to get an aggregate for you in the period of time that we had.

DR. DUNN: Thank you.

Questions to the Committee and Discussion

DR. NARENDRAN: Now, we will move to the committee discussion.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the

public comments. We will proceed with questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We'll proceed with our first question, which is a discussion question. Discuss the strength of evidence provided by the two phase 3 studies, 00071 and 00072. In particular, discuss the impact of the discordant results on your overall assessment of efficacy.

Are there any questions about the discussion question or it's pretty clear?

(No response.)

DR. NARENDRAN: Anybody volunteering to go first? Dr. Shiner?

DR. SHINER: I will say that they are both very well done. I agree that one is very strongly positive; one is very strongly null. Considering

them together, I don't know whether the combination of brex plus sert is better than sert alone because of the discordance.

DR. NARENDRAN: Dr. Simon?

DR. SIMON: Greg Simon from Kaiser Permanente Washington. What's notable to me is that across those two trials, we see a similar, at least, mean change in CAPS scores with combination treatment. The difference between them is the greater improvement with sertraline only or sertraline plus placebo in Trial Number 072. So I think that's where we have to look to explain the difference.

We don't see a difference in the design that might account for that. There are not differences in the execution of the trial that we're aware of, differences in the eligibility criteria. There are no differences, major differences, in the patient characteristics that were measured or reported, except it is true that there is a slight difference in the proportion of patients who had previous exposure to pharmacotherapy, or to SSRI

pharmacotherapy, between 071 and 072, and that does go in the direction of at least a speculation that Trial 072 may have enrolled a population that was more likely to respond to sertraline.

My overall assessment is that this is a heterogeneous condition, and that even by chance, trials could enroll quite different populations with respect to the underlying clinical heterogeneity. We at this point know that there's wide variation in how individuals respond to sertraline, how people with PTSD respond to sertraline. That is, at least to my understanding at this point, not explainable or predictable, but we know that variability exists, and I suspect it's that heterogeneity we're seeing.

So I'm interpreting that the results of those two trials, Trial 071 shows us that sertraline plus brexpiprazole is a superior treatment in a population that has a relatively poor response to sertraline, and Trial 072 shows us that sertraline plus brexpiprazole has a relatively weak effect in a population that has a high

probability of response to sertraline; and they're probably two different populations, even though that's not directly measured. I need to be clear that's my speculation, but that's how I'm understanding it.

DR. NARENDRAN: Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA. In regards to Trials 071 and 072, I don't have any major concerns as far as interpreting the data. 071, as has been stated, clear that it met its primary and secondary endpoints; and for 072, clear that it did not. And that's really not, I think, the main focus of my concerns.

The only thing I would say that maybe is of relevance is just the questionable clinical advantage or relevance of this 5-point difference. I think it's important to remind everybody that the controlled condition was not placebo. This is a benefit that you can get with an SSRI alone. And then probably part of the later discussion is, is that 5-point benefit worth the potential adverse outcomes that you will get with addition of an

antipsychotic. But overall, 071 positive, 072 negative, so I think, for me, it really comes down to how we look at 061.

DR. NARENDRAN: Dr. Ballon?

DR. BALLON: Jake Ballon, Stanford University. Echoing a lot of what has been said, but I think, reflecting, the difficulty of this conversation was clearly evidenced in the public comment being very much split; and that even within some of this discussion already, reflecting that this is a tough one to adjudicate because, really, we have two things that are in direct conflict. And it's going to come down to, to some extent, weighing the negatives of one versus the potential positives of another.

I think, for me at least, when I'm looking at these two studies, similar to what Dr. Simon was saying, I feel like the consistency effect of the combination treatment across all three studies is compelling to me, and the notable increase in the comparator groups effect in the third study, largely driving this potential conflict, one can't

necessarily completely move that aside. But it does, to me, give a little bit more credence of the possibility of 071 closer to being maybe more than what's happening, and that these combination treatments are potentially effective.

DR. NARENDRAN: Dr. Block?

DR. BLOCK: Hi. This is Laura Block, patient representative. I really liked what Dr. Shiner had to say about it being null versus negative; that is, 072. Yes, we didn't meet the planned response. We did not get a difference between placebo and treatment. And I know I was taught never to compare across studies because they're all different, but we do see a fairly consistent response in the CAPS-5 across all three studies. And as a patient, I want to see the benefit.

As to whether or not it's worth it, when you look at the side effect profile, that's a heart decision that the patient and the doctor need to make together. And the answer to that for each patient may be different based on what's going on

in their life and where they are in their disease and their life. I really, again, like the idea that one of the other speakers said about having that bigger box of tools. That's the end of my comment.

DR. NARENDRAN: Dr. Coffey?

DR. COFFEY: Yes. To kind of reiterate what others have said, but maybe focus on the way the question's worded, I think the big challenge here is if you look at them both in isolation, the strength of evidence is strong for 071 and 072; it's just going in opposite directions.

I think when you look at the bigger picture -- and this is what I'm struggling with -- it's similar to what Dr. Simon said. It was pointed out that in the original sertraline studies, two of the four were positive. So if you look at that, it may not be that surprising that one trial has a larger sertraline effect than another sertraline effect, which may also get to Dr. Simon's point of, if you're in a population that responds to sertraline, the combination

doesn't work that much better. If you're in the population that doesn't, it does. I mean, I kind of had the same thought when you mentioned that.

Where that gets complicated here in terms of the overall assessment of efficacy is balancing there's a group that could benefit from this and a group that would not benefit but would have the additional risk. And I think that is really the crux of the problem that really has to be broken down here, based on these two phase 3 clinical trials.

DR. NARENDRAN: Anybody else online, virtual?

DR. RASKIND: Yes. This is Murray Raskind. Can you hear me?

DR. NARENDRAN: Yes, I can hear you, Dr. Raskind, good.

DR. RASKIND: Okay. I'm not sure where I'm supposed to be in the seating chart, but thank you for requesting the input.

I'd like to make a few comments from the point of view of a clinician, a practicing

psychiatrist working with mostly combat veterans and active duty military. I appreciated the comments of the veterans who spoke. They were from the heart and moving. But it pointed out to me, a representative, a sample within these samples, of veterans with combat PTSD. They essentially didn't exist in the trial. So, for me, it's going to be difficult to extrapolate these already confusing contradictory data sets to my clinical practice. And I know this is a bit of a soapbox, but I would urge as a group to, over time, consider the differences among military combat PTSD and civilian PTSD, as well as the overlaps, but keeping this in mind when studies are designed and executed.

Secondly, I'm not sure we're adding a new tool to our toolbox. We already have sertraline. We have brexpiprazole. The prescribing physician, nurse practitioner, whomever, can make the decision, based on the data that have been published and the literature, as to whether they want to progress to a combination or start with both drugs at the same time. Although I must say,

in my many years of practice, combination drugs have presented complexities in terms of adverse effects and trying to figure out which one of the components of the combination medication preparation is the problem. So just those points, and I realize that doesn't speak to is this effective or is it non-effective.

Finally, in terms of adverse effects, weight gain is a big deal, at least in the veteran PTSD population, weight gain secondary to antipsychotic drugs. This is not a small adverse effect and has important implications for long-term cardiovascular health, so I don't want that to be trivialized. I'm still looking at these studies, not convinced that the combination offers, at least me as a clinician, a new tool.

DR. NARENDRAN: Thank you.

DR. RASKIND: Thank you.

DR. NARENDRAN: Thank you, Dr. Raskind.

Dr. Shaw, virtual panel?

DR. SHAW: Thank you very much. Dr. Shaw. Yes, the way I think about this question is, 071

and 072 were designed to answer a very specific question about efficacy, the very specific question being, is the combination of the brex-sert over monotherapy of sert, is that superiority? Can we establish that in the general population of patients with PTSD of a certain severity? And them being very well-controlled trials, one being resoundingly positive and one being resoundingly negative, they aren't together giving convincing evidence of that very specific question of efficacy.

The discussion I'm hearing a lot about is thinking about other questions of efficacy. Is it that we hypothesize that there's a certain subpopulation that may be responding better to the combination than, say, sertraline alone? But those experiments were not done, and we don't have the evidence. If we wanted to ask the question, for people who failed the monotherapy, will this combination be of benefit, we did not study that population. I've heard that population may make upwards of 60 percent of the patients, but we

didn't identify those folks to be able to figure out if this is safe in that population.

Sometimes, as we've heard from Dr. Raskind, the combination therapy, the AEs can be difficult to disentangle. We don't even know if there's something about the genetics of the responders who don't respond to sertraline that maybe they have some higher risk of one of the AEs, and that's why we might study a particular population if we wanted to answer that other question.

So I think about 071 and 072, not about what is the potential in the big world of how the combination may be helpful, but what was actually studied and what did we get evidence for. And we were very specifically studying 071 and 072, this combination over the monotherapy in the general group of patients that doctors then might just prescribe this to. And for me, because they were in direct conflict, these two studies as confirmatory trials, they do not add up to answering that question, or I should say that they do not provide sufficient evidence to conclude

there was efficacy there over the monotherapy. Thank you.

DR. NARENDRAN: Dr. Fiedorowicz, if you want to weigh in.

DR. FIEDOROWICZ: I don't have much add to question 1 because I thought one study was unequivocally positive, and the other was unequivocally negative, and there didn't appear to be any compelling evidence to explain those discordant results.

DR. NARENDRAN: Yes, my thoughts were sort of on the similar lines of, I think, the last two panel members; that 071 and 072 are well done, but being so discordant, I don't know how to use 072 to interpret 071. That's how I would come on, on that side.

Anybody else want to add anything else?

Dr. Canuso?

(Dr. Canuso gestures no.)

DR. NARENDRAN: Okay. Then, I'll summarize what I heard.

From what I heard, both studies are really

well done. One is clearly positive; one is clearly negative. I heard that, possibly, some panel members thinking that 071 is probably more accurate, and maybe the reason 072 failed is probably because of the heterogeneity in the PTSD population. I heard that, possibly, the combination could work better for people who have a poor response to sertraline as opposed to the combination may not be as effective in people who have a better response to sertraline. I also heard that although there may be genetic factors or response factors that might drive the different results, neither of the trials looked at that, particularly, to provide that data and is another viewpoint of some of the panel members. In general, I also heard they we'd like to hear more broader inclusion of military populations, to be included.

Do you want to add into it, Dr. Simon?

DR. SIMON: I wasn't sure exactly what you're referring to, but the point being we see this discordant result I suspect likely

representing differences in the patient populations, which we cannot exactly measure. But I would not want to go on record myself as saying I think that Study 071 is a more accurate reflection of the true population than 072.

DR. NARENDRAN: Sure.

DR. SIMON: I think they're probably different. I think we know there is considerable heterogeneity, and that add mixture likely varies across different clinical settings and across different patient populations. It would be nice were it measurable or predictable in advance, but it is not.

DR. NARENDRAN: That makes sense. Thanks for clarifying.

DR. SHINER: I would also like to reflect to Greg that that would be an amazing coincidence had all of the people who respond to sertraline alone been randomized in 072, and all the people who tend to respond poorly to sertraline alone --

DR. NARENDRAN: That should be a future study.

DR. SHINER: Yes.

DR. NARENDRAN: Anything else? Anybody else want to weigh in or correct things for the record?

(No response.)

DR. NARENDRAN: If not, we can move to question number 2.

Question number 2, discuss your view on the contribution of Study 00061 on the overall evidence of effectiveness. Does anybody have questions about this question?

(No response.)

DR. NARENDRAN: I know Dr. Dunn had a little clarification.

Do you want to add it?

DR. DUNN: I'm going to pose this to my statistical colleagues on the panel.

Given that they ran the new model, then it appears that they actually get a little bit of a more significant effect for subjects in 061 who had prior SSRI use and exposure, I think as I mentioned before, my concern is that this is a proxy for treatment resistance. Unfortunately, we don't have

the E-TRIP numbers.

Based off of how how that statistical model works, would it be accurate to conclude that a history of SSRI use does not mitigate the effects of the combination drug, and that that imbalance actually doesn't pose a problem in terms of that comparison?

DR. COFFEY: You're referring to the model?

DR. DUNN: Yes, the new model that they ran.

DR. COFFEY: I think it strengthens the argument. I would like to see them fit a treatment by SSRI use interaction to make sure that there wasn't any differential effect based on SSRI use, which the control of the covariate does not explicitly do. So it's a step in the right direction, but I don't think it completely rules it out.

DR. SIMON: Yes. I would strongly agree that I think the question there is not a confounding but an interaction question. The question is, if those who had previous exposure would be entering this trial -- my presumption is

those who had previous exposure to one of those treatments, and it performed very well and had no adverse effects, would not be candidates for this trial because they would still be receiving that previous treatment.

So having received a previous treatment and still seeking treatment through this trial is probably a marker for that previous treatment was not that helpful. So to the extent that we were overenrolling people who had previous unsatisfactory exposure, that would disadvantage sertraline in such a setting because you'd be selecting those people, I think. So it's an effect modification or interaction question, I think, not a confounding question.

DR. DUNN: So that that model they ran does not address that potential problem that the sertraline-only and the placebo group, both of which had a higher percentage of SSRI exposures, were disadvantaged or handicapped because they were treatment resistant. That new model they ran does not address that concern.

DR. COFFEY: I don't think it completely addresses it. I mean, the fact that they controlled for it and it didn't modify the endpoint helps some, but it doesn't directly affect the effect modification question.

DR. DUNN: Thank you.

DR. NARENDRAN: Dr. Shaw, I think you concurred.

DR. SHAW: Yes. Thank you. I think my hand times out. I have it up, and then it goes away.

Pamela Shaw. Yes, since there was direct callout to the statistician on the panel, I wanted to add that I agreed with Dr. Coffey who spoke, that it really seems like the interaction is the question to be thinking about and not just the way the model was presented. So I concur with all the statements that were just made, and I just wanted to put that on record.

But I also wanted to point out, in addition to this idea that we think there may be responders and non-responders that are difficult and may have proxies for who we think they are, I do think that

there is something to be said for why this population, in general, those with PTSD, are hard to study because there is some heterogeneity in the patients' experience with the severity of their symptoms at any given time. So I do think that that can play a role. Twelve weeks isn't a long time, and maybe for some patients, they maybe are in a long triggering event that is difficult to treat, or that they're responding to stimulant, or creating a more heterogeneous response even within those subpopulations.

So I think it is difficult to disentangle, without doing genetics and other real experiments, why a particular trial may be in conflict with others. So it may likely be more complicated than simply there are responders and non-responders. There can be times in a person's life when they are much harder to treat than other times, but given the stimulant going on, other challenges. So I think it could very well be, in some sense, that these trials are underpowered from the point of view of not thinking about that serial correlation

and response, and how that might add more variability than you were planning on in how patients do respond to a therapy or or not. Anyway, those are just some thoughts.

DR. NARENDRAN: Thank you.

Just going back to this question, we'll focus back on question number 2, the discussion question. Discuss your view on the contribution Study OO61 on the overall evidence of effectiveness. So do people want to weigh in?

Dr. Shiner, let's start with you.

DR. SHINER: I guess this is more of a question. I see this question as really being about the rules that a pharmaceutical company can expect when they participate in this process. And if they've met the criteria, their drug should be approved; if they haven't met the criteria, their drug should not be approved.

So hearing from FDA colleagues, it sounds like two positive pivotal trials would get you approved, but there are some cases where there is a strongly positive phase 2, and then the FDA says,

"Well, it would make sense to only have to do one pivotal trial because it's been so positive, and it will be hard to do two pivotal trials."

It doesn't sound to me like this was the case here. It sounds to me like there was an exploratory trial that allowed the company to decide what comparisons they wanted to make rather than a strongly, strongly positive phase 2 trial, and the recommendation to do two pivotal trials, one pivotal trial was negative and the other pivotal trial was positive, and then there was a backwards look at the phase 2 data.

I don't get the impression -- and please tell me if I'm wrong -- that this meets the normal criteria for not having two positive pivotal trials. So in my own opinion, based on my understanding of what you just said, I don't feel all the questions about 061 aren't even relevant because I don't feel that we can include the data.

DR. NARENDRAN: Go ahead.

DR. BURACCHIO: Hi. This is Teresa Buracchio. I was just going to address the comment

about the rules. I don't think we would consider them rules; they're more guidelines, ways to think about the data, good practices. But we do consider the data itself, and we also consider it in the context of the disease. We are dealing with a serious disease. We are dealing with a disease that has unmet need. There are some approved therapies. There is need for more tools in the toolbox, so to speak. So we do consider that broader context.

As I mentioned earlier in one of my earlier comments there, we typically look for really rigorously designed studies with prespecification of outcomes, and hierarchical or control for multiplicity, but there can be situations where we can find the data so persuasive, or the need so great, that we are able to be flexible and consider that data in the broader context, and perhaps give it more weight than we might have if we didn't have those other contexts.

So it an art, I would say, to sometimes say can we meet substantial evidence of effectiveness

or not? So I just want to get away from the idea that there are absolute rules. There's what we typically see, what we would typically expect, best practices, but we do want to take the context of the disease and the data that we have in front of us.

DR. NARENDRAN: Thank you.

Dr. Ballon?

DR. BALLON: Jake Ballon, Stanford University. I feel, to use maybe like a sports analogy, this is like the World Series. We've gone back and forth, and game 1 went to 071, and maybe that went to two or three games worth, and now we're going back and forth.

So we're in the seventh game, and it's tied, and we're getting towards the end of the game. Did 061 hit a grand slam to win the game? I don't think it did, but did maybe somebody kind of walked across the plate and just enough?

I think, for me, I hear back and forth Dr. Dunn and treatings around the sertraline response, and I think those are very compelling and

concerning. I hear concerns about, well, did the sponsor adequately make a statistical plan in advance or not, and there are discrepancies between the FDA's view and the sponsor's view. My take on that is maybe that was poor communication rather than malfeasance, and when the statistics were being done by the company, they had done a prespecified plan, and they just maybe hadn't communicated it well. So I kind of give that one towards the finding as opposed to being suspicious of the finding.

So when all is thrown into the wash, to me, we do see that there was a pretty reasonable finding in the direct comparator arm, the one that we're looking at, in comparison to 071 and 072. So while it's not a slam dunk, to mix sports metaphors, it is, to me, just enough over the line to be compelling.

DR. NARENDRAN: Dr. Coffey?

DR. COFFEY: Yes. Chris Coffey. So I'll take a slightly different sports analogy view on that. In my mind, 061 is like the close scrimmage

college basketball teams do before the season starts, where it gives you evidence on the team, it's very informative, but it doesn't count for your NCA tournament selection criteria.

So the challenge that I see here is I think 061 was a good study. It provided evidence of effectiveness. And I think if only two studies in front of us were 071 and 061, this would be a different discussion. But in my mind, 061 supports the effectiveness that 071 showed, but it can't offset the negative -- let me reiterate that.

In my mind, 072 and 071 were positive studies in that they answered the question they were set out to do, definitively; they were just in different directions. And I'm struggling with how 061, given that Study 072 exists, could offset a study that did not answer the same question that 071 set out to do.

DR. NARENDRAN: Dr. Shaw?

DR. SHAW: Hi. Pamela Shaw. I would like to say just two points with respect to this. And I hear a little bit of an echo. I'm not sure if

other folks are muted or -- do you hear the echo or is it just me?

DR. NARENDRAN: We hear you. No echo.

DR. SHAW: Okay. Great.

What I'd like to say is that with respect to 061, there's a lot of discussion about the false positive rate and how to handle those p-values, and the company made a reasonable presentation. The things that I think are objectionable statistically is, were there five p-values, or were there three p-values? In one argument, there were four p-values; what corrections should we make?

But that type 1 error discussion is really not the question we had. The experiment that is being put before us, that we need to worry about that type 1 error rate, is we're going to do two studies -- for the sake of argument, we're going to call them 071 and 072 -- and we're only going to accept the results of those studies if they're both positive. And if one of them is negative, we're going to look to the past and take something that's not random that we already know is in the bag, and

we're going to use that instead.

So that is why I think a lot of folks, particularly Dr. Coffey who just spoke, and others are having a really hard time figuring out how 061 could be added into the evidence formally to somehow negate 072 or even be admitted. I think our first speaker was concerned that they couldn't even look at it, and I think that's why; because that is the operating characteristics that a statistician is thinking about, is that post hoc, decision making that is, is questionable.

Now, this is a situation where it's a serious disease, there's a high unmet need, so we can we think outside the box, and we've heard that a couple times today. For me, it can't be what I feel like a lot of folks are thinking about; okay, score 1 for 061, score 2 for 071, and then we've got this 3 to 2 to 1. That's not the right way to handle the data.

So I don't think we can say, "Hey, we've got two positive and one negative." We'd have to take more formal meta-analysis considerations, and even

if we could forget about that post hoc nature, the resounding null of 072 means when you put it together statistically with 071 and 061, they're not going to add up to convincing evidence statistically. But we certainly can't simply negate 072 and say, "Hey, we're going to approve this drug based on two trials, O61 and O71." That I have huge problems with. We have to think about all three studies in that respect.

061 was very encouraging, but it can't, by itself, put us -- and what was the sport's analogy -- over the plate. It just doesn't add up to convincing evidence across the three studies, considering how null one of them was. I don't think there's any meta-analysis that could be done to come up with evidence that would be near what we usually use or think about. So there's just a big open question right now about the value of the combination of the monotherapy, in my mind, and O61 didn't help answer it. Thank you.

DR. NARENDRAN: Thank you.

Dr. Raskind, virtual?

DR. RASKIND: Yes. Hi. Thanks for seeing me long distance. The issue of context I think is important here because we're dealing with a situation where both of these drugs are available. To me, having some evidence from one study and looking at other sources for a new drug, that otherwise would never see the light of clinical day if not approved, would move me more toward a less rigorous evaluation.

But here we have two drugs that are not going to go away. We've got them. And if a clinician wants to use those drugs in combination, or use them sequentially and the second as adjunctive if the first did not provide reasonable clinical benefit, which would be my choice, that's available in the clinic. So it's not like we're deep-sixing brexpiprazole, which is a good antipsychotic, atypical antipsychotic, and it's there on our formulary if I want to use it in combination with an SSRI. So I'm leaning toward the more rigorous standard for this proposed combination medication, and thank you

DR. NARENDRAN: Thank you, Dr. Raskind.

Dr. Simon?

DR. SIMON: The specific question of what does Study 061 add, I think we've heard some concerns about changes in the analysis plan, which would put it in the category, to me, of modest rather than convincing evidence. But also, I need to add the qualifier modest support for the effectiveness of the combined treatment over sertraline alone in a population where sertraline alone did not work well. The other thing where Study 061 stands out is sertraline is essentially equivalent to a placebo in that study population.

DR. NARENDRAN: Let's hear that again.

DR. SIMON: They're clearly looking at the history of sertraline trials. There are some patient populations among which sertraline works well and others among which sertraline works poorly. Study 061 was a population, for whatever reason, in which sertraline worked poorly, so the combination treatment seemed to have modest evidence of its effectiveness there. Had it been

by chance, as would be in some of the previous sertraline trials, a population where sertraline worked very well, I doubt we would have seen any advantage.

DR. NARENDRAN: Makes sense. Thank you.

Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA. To follow up on Dr. Simon's comment, when I looked at 061, the first thing that jumped out at me is why did the sertraline, our active comparator, did not separate from placebo given that that is the primary comparison that the sponsor is seeking? It did not behave as expected. And there's been discussion about assay sensitivity, and even though they did, quote/unquote, "detect a difference," how much can we trust that difference? Is it a spurious result?

Then, the next kind of logic is, well, why didn't sertraline behave as expected? And one possibility that I've been reiterating over and over again is that the subject population is different than the combination population, and, potentially, they have a higher treatment of

resistance.

So it sounds like we've moved in the right direction but we haven't gotten the definitive answer, unfortunately, and we're probably not going to get it today. I think the E-TRIP numbers would have helped to see that either the presence or absence of resistance was comparable between the different arms.

Then further beyond that, there are some aspects about the E-TRIP questionnaire that are problematic. For example, this threshold of 8 weeks of treatment before you get a score, before it's recognized that that was a failed treatment, I think as most clinicians would probably agree, that's a long time to ask a patient to stay on a medication that is clearly not working.

So I think with all those things taken together, that's a big X against 061. I don't think it's a fatal flaw, but certainly it is something that would keep me from saying that 061 shows definitive superiority in the combination treatment over monotherapy.

The other things about the statistical analysis plan, I'll certainly defer to my statistical colleagues on that. But, again, these are all things that bring into question how much can we trust the outcomes for 061. Then again, looking at how much of an advantage, even if we say that, okay, we trust the results but we're looking at a 5-point advantage over monotherapy alone, which presently is standard of practice, should we deviate from that? I don't know if the evidence across both studies compels us to do that.

As Dr. Simon mentioned, there's potentially a differential response. That's something we can't predict a priori, so we have to go through the exercise of trying the monotherapy first, and if it doesn't work, then we can potentially move to a combination treatment. But that's not what these studies were designed to look at. These studies, the label, the indication that is being sought, is, start a combination treatment without any evidence of any SSRI failure. Thank you.

DR. NARENDRAN: Dr. Thomas, who is virtual.

DR. THOMAS: Sorry. I just wanted to get to the question of the contribution of overall effectiveness. I don't know, given some of the statistical concerns, as well as the population that was chosen, that it would amount more to trend data, at best. And we probably wouldn't even be discussing it at that level, that it wouldn't be brought, if the level of need weren't so significant that you would have to look for something like that. But as to whether that swings the balance or not, that's what question 3 is going to be about. But I'd say, in terms of this contribution, it's low to very little.

DR. NARENDRAN: Thank you.

Anybody else want to weigh in? I think we've heard a lot about 061.

From my own personal opinion -- Raj Narendran -- I also feel it's very difficult to substitute the effects of this trial given the statistical issues. It was really an exploratory trial, so it was to give you hypothesis. And now to go back and try to understand how much it

contributes, to substitute for substantial effectiveness, I just don't think I can do it based on this.

To move on to discussion, I heard a lot of people concur that it's difficult to use 061 to determine the drug's effectiveness in itself or substitute for 072; however, I heard that it does indicate, modestly, low to moderate, shows that the combination is effective.

I don't know how that helps in terms of the agency. Does that make sense? It's a judgment call. Sorry.

Next, we'll move to question number 3. Based on the available data, and with consideration of the known risks of brexpiprazole and sertraline individually, discuss the acceptability of the proposed concurrent initiation treatment paradigm.

Anybody want to go first? Dr. Simon?

DR. SIMON: First, a question about the question. That sentence, there's no period there, so I wanted before the end of it to be, "compared to what?" This would be meaning compared to the

current state of nature, and going back to what Murray Raskind said a few minutes ago, the current state of nature being sertraline available, approved for treatment of PTSD; brexpiprazole available, sometimes prescribed, but not officially approved for this purpose. So we're seeing acceptability of the combined treatment being an approved indication compared to this state of nature, not compared to nothing.

DR. NARENDRAN: I'll let agency answer that clarification.

DR. MANTUA: Yes. Valentina Mantua, FDA. We're asking, in terms of concurrent initiation, in other words as a first-line treatment. So that would be a patient comes to you, and you give both the drugs together. In the context of available evidence, this is what was discussed in question 1 and 2.

DR. FARCHIONE: Yes, the lack of a period is just a typo.

DR. NARENDRAN: Dr. Block?

DR. BLOCK: Laura Block, patient rep. While

I don't feel comfortable with the p-values because of maybe when the analyses were chosen, but I see a trend in 061 that looks good. And then I see 071, which is everything it's supposed to be. And we can't really understand why everybody improved with 072. But everybody in every test, or in every assay, every trial, we see that the patients are improving. And as a patient, that sounds pretty good to me. And when I look at the side effect profile, yes, there are some significant side effects there, but they don't really overlap very much. So if one of them causes a problem because we started them at the same time, it's likely to be fairly clear who the trouble child is, and then make adjustments that way. That's it.

DR. NARENDRAN: Dr. Ballon?

DR. BALLON: Jake Ballon, Stanford. First of all, I really appreciate the conversation that we've had, and Dr. Shaw and Dr. Coffey, the statistical analyses have been really helpful for, again, thinking about this on-the-line kind of question here.

I think when it comes to this question, the idea of concurrent initiation, Dr. Raskind's point, has been echoing throughout my head, throughout, which is these medicines already exist. And I go back and forth in thinking, well, this is not an Otsuka advisory board meeting where we're advising them on how to make a study, or how to sell a drug, or whatever, and should this combination be approved or not. The question is not whether or not I would use it, or would rather actually start with sertraline first and then see if it failed -- which is probably what I would do in my clinical practice.

But I think the part that Dr. Raskind brought up that I think has also been helpful for me thinking about this, too, is this idea that since that already exists, since this is something -- again, we aren't really adding anything new to the armamentarium. We're giving an imprimatur from the FDA, potentially, that says this works. But the data is out there. People can make their decisions, and they can use these

medications how they want.

And there's nothing in the proposed studies that is using different dosages of the medications that wouldn't otherwise be available like we see with some combination pills, where, okay, maybe you would really only want a tiny little bit of one of the medicines that had standard dosing or standard packaging, and you couldn't achieve that. Here, everything that we have discussed is achievable in the clinic already. So the idea that that raises a little bit the standard as to whether or not a combination pill should be approved is important.

I think, for me, also, as a person who predominantly treats schizophrenia, where I think of Rexulti as a low-risk medication compared to some of the other medications that I use, as I zoom out and think about Rexulti versus the other proposed medications for PTSD or for depression, weight gain, akathisia, and the like, suddenly take on a different level of risk than I am otherwise accustomed to thinking about when I'm thinking about Rexulti as a medication, and that also

changes things for me as well.

DR. NARENDRAN: Thank you.

Dr. Dunn?

DR. DUNN: Walter Dunn, UCLA. For this question, I'm interpreting it primarily as the risks and the potential adverse effects of this combination treatment. I think most clinicians would agree that across clinical trials, the adverse effects are vastly underappreciated, and once we put them into clinical practice, when these patients are on these medications for years and years, we really see a lot of weight gain, and we see a lot of tolerability problems that were not reflected in the pivotal trials.

So I think, overall, the big question for me is knowing that antipsychotics can cause real problems, especially with long-term use, and the modest benefit that the combination treatment potentially can offer -- again, that's with a big caveat because I don't actually even know if there is really a benefit. But again, given the benefit of a doubt, even if we give them the 5 points, I

actually don't know if all that weight gain and potential EPS problems and TD is worth that.

I'd be interested to have a conversation with a patient and lay it out in front of them to see if that's something they would be willing to accept without even trying sertraline first. So that would be one of my main considerations here.

The other thing is that even if we got the label, or even if the sponsor got the label, how would this play out in clinical practice? How would this play out with the payers? As Dr. Raskind pointed out, we are really not adding an additional treatment option; these things are already available. Perhaps a label would compel third-party payers to cover this.

I would have a hard time believing that third-party payers would cover this as a first-line therapy. They are probably going to require some type of failure first of an SSRI before covering brexpiprazole. And then we're in the space of this is actually not the population that these studies looked at, so none of this data would be supportive

of that deployment of brexpiprazole.

So I think, again, that's out of the scope of the FDA. This is real-world considerations, but those are the things I'm thinking about when considering if this should be a label for a first-line treatment.

DR. NARENDRAN: Thank you.

Dr. Simon?

DR. SIMON: To me, it's interesting to think about the references today, the history of sertraline's approval for treatment of PTSD, where it took four trials to find two that were positive; yet, a 50 percent hit rate, pretty much the same here, except we have one in one. And sertraline passed, but I think the fundamental difference is sertraline was the first pharmacotherapy approved for treatment of PTSD, so it really wasn't a situation where we got this or nothing; while this situation, going back to what Murray Raskind has reminded us of a few times, that's really not the situation here. We're not talking about this or nothing.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz, who is on virtual.

DR. FIEDOROWICZ: Thank you. Jess Fiedorowicz, University of Ottawa. Related to the question about concurrent initiation, that does raise some concern, as was raised by speaker number 7, Kim Witczak, talking about the risk of adverse events. But I think it's worth noting that, on the other hand, many patients with PTSD will have had prior treatment trials, and combination drugs aren't precedented. And for better or worse, starting two drugs does happen in real-world practice.

I think the things that would be especially compelling to make a rationale for a combination drug would be either evidence of synergy, and that could be theoretically through some sort of biologically plausible mechanisms; or empirically with direct testing of synergy such as if we approach the analysis of 061 as a two-by-two factorial study, which it doesn't look like was part of the approach of the plan; or ideally both,

evidence of biological plausibility and empirical evidence to support. And I guess the other piece that would be compelling is if there was some rationale that the combination mitigated toxicity in some way, which I don't think we see here either.

DR. NARENDRAN: That's great. Thank you.

Dr. Shaw, who's virtual as well.

DR. SHAW: Yes. Thank you. Pamela Shaw. Really, actually, I will make my comments shorter because I think the last speaker was really well spoken, the last two speakers.

We have a different standard for approving a combination because of some of the risks that are added on, that we would want this drug to be superior in some way. They're more safe and more efficacious than the monotherapy alone. So that's the efficacy that I'm thinking about.

I guess the second point is, what I hear from discussion of clinical practices is how it might likely be used is in a way that it was not studied, in that people would be thinking about,

"Oh, this person did not respond to sertraline alone, so I'm going to add on this other thing," and that a label, also what I heard, would encourage that behavior, as something that you should think about. So that makes me very nervous about a label when we think, if the bar for a combination really should be that combination needs to add something over monotherapy.

So -- I think the conversation started with Greg -- I wanted something after efficacy in this discussion question. It's a very specific kind of efficacy I think we need to think about for combinations, which I think is some of the themes of the comments here. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thomas, who is virtual as well.

DR. THOMAS: Yes. I think it's been summarized pretty well before, is that given how this would actually be used and whether it's above and beyond what's already available, and that there are existing things going on, it's unclear to me that it rises to the standard that you would need

for a co-initiation.

DR. NARENDRAN: Thank you.

Dr. Raskind, do you want to add in, virtually?

DR. RASKIND: No, I think I've already caused enough trouble.

DR. NARENDRAN: Thank you, Dr. Raskind.

I will try to summarize this. I don't have much to add other than what was elegantly said.

So what I hear is, in the real world, co-initiation may not be a preference of how people will use this. People may still be forced to start sertraline and then add brexpiprazole. Third-party payers may enforce that. A patient's preference may allow for that. I also heard that co-initiation could lead to, in the real world, a lot more risks related to the brex in the population of PTSD, unlike in a psychotic disorder population, which is much more attuned to using these medications that could cause weight gain, akathisia, EPS.

I also heard that the efficacy of the

5-points benefits in itself doesn't give people the thrust to think that they would co-initiate, the clinicians who'd start it, because the efficacy is not really solidly shown. So that summarizes question number 3.

We will now proceed to question 4, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed the vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue

in the same manner until all the questions have been answered or discussed.

The voting question is, based on the available data presented, has the efficacy of brexpiprazole, when initiated concurrently with sertraline, been established for the treatment of PTSD? Please provide your rationale and indicate the specific information on which you base your vote, after the vote.

Any questions about the question? It's pretty clear.

(No response.)

DR. NARENDRAN: If there are no further questions or comments concerning the wording of the question, we will now begin the voting process.

Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or wish to change your vote, please press the corresponding button again before the

vote is closed.

(Voting.)

DR. FRIMPONG: Joyce Frimpong, Designated Federal Officer. For the vote, there's 1 yes and 10 noes, and no abstentions.

DR. NARENDRAN: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did, for the record.

I'll start with Dr. Coffey.

DR. COFFEY: Yes. Chris Coffey. I voted no. In essence, while I feel like Study 061 supports the effectiveness that Study 071 showed, it really doesn't offset the discordant finding from 072. So I don't think it reaches the level to say that it has been established at this point, based on the totality of the evidence.

DR. NARENDRAN: Dr. Simon?

DR. SIMON: I voted no. I believe that Study 071 is supportive, Study 072 is clearly negative, and Study 061 can only provide suggestive

or modest evidence. So I don't believe that the efficacy has been well enough established.

DR. SHINER: Hi. My name is Brian Shiner, VA Vermont Healthcare System. I voted no because, in my opinion, looking at 071 and 072, it's just as likely that the drug does not work when added to sertraline as it does, so I don't think it's worth the risk.

DR. NARENDRAN: Dr. Ballon?

DR. BALLON: Jake Ballon, Stanford. I voted no. I went back and forth a lot. I came to this hearing, having read through things, thinking I was on the fence but leaning towards yes. I think, having listened to all of this, I'm compelled to think about legal standards and, to me, I think we have probable cause to believe that this combination pill works, but I'm going to need at least preponderance of the evidence, maybe not necessarily beyond a shadow of a doubt, but certainly preponderance of the evidence to be able to do it, and this doesn't quite get there for me.

I do, though, want to really recognize the

public comments, particularly around the need for more treatments, and to make make it very clear that I share that opinion; that I recognize that it is difficult to find treatment, particularly in rural areas; that this hearing is largely focused on psychopharmacology when, in fact, psychotherapy treatments can be very effective for PTSD. And while that can be difficult to replicate, there were very few people who'd received psychotherapy in any of these trials, and that is important. Written exposure therapy and many other types of therapies can be very effective. So I want the folks who are maybe disappointed perhaps by this vote to keep that in mind.

I know that people have been through a lot, and they've tried a lot of different things, and the idea that we were going to get a new medication perhaps might be disappointing. We have talked about how these medicines do exist; that this evidence with probable cause of being effective would be compelling to prescribe off label, in a way that it wouldn't have been that way without

some of these studies; that it frames a conversation around side effects, and risks, and step-wise progression of treatment in a more interesting way than if we hadn't had any of these studies; but that it isn't the slam dunk that I would want to start both of these medicines together, nor do I think that that's a really safe and purposeful treatment. So I just want to make sure that that is clearly articulated and on the record.

DR. NARENDRAN: Thank you.

Dr. Block?

DR. BLOCK: Laura Block, patient advocate. While both of these individual component drugs are on the market, a third-party payer isn't likely to pay without an FDA-approved indication. So that means that there are those who are going to have difficulty accessing this before it is approved. And those who can't afford to pay out of pocket, I hate to think that they might have to wait another four years to see something happen.

I do want to be certain that we don't offer

destructive false hope. I would love to see, no matter whether this is approved or not, either a phase 3 or phase 4 study with 12 weeks at a stable dose to see do those numbers continue to trend; does the CAPS-5 get better over time; and maybe even have a control for the kind of therapy that's offered. Maybe there's a modality and a small stable of practitioners that are offering therapy using telemedicine to help control another variable, and maybe also the genetic tests that you all had talked about. I would love to see what that were, to look at. Thank you very much.

DR. NARENDRAN: Thank you.

Raj Narendran. I voted no. I struggled a lot with this as well. I felt like one trial looked so promising, and the other, just trying to find something in the phase 2 trial that could convince me that it could work. I think the reality is another phase 3 trial is what's necessary, which is identical to 071 at this point.

DR. DUNN: I'm Walter Dunn, UCLA. I voted no. I'd like to start by saying I'm a strong

advocate for increasing treatment options. This is something that our field lacks, especially tools that really differentiate themselves and aren't just another me-too drug. So as Dr. Buracchio mentioned, if this was a significant major advance, I think I would think a little bit differently about it. This approval process is an art. There are not strict guidelines as far as this is what you definitely need to get approval. I think I may have been swayed if, again, this represents a major advance in the field. At best, I think it's potentially incremental.

Even if 071 and 072 were positive, unequivocally positive, I would still take pause as far as how this would change our practicing guidelines. As Dr. Simon mentioned, this is a heterogeneous population, and even if we demonstrate a 5-point improvement, which is, potentially, not even clinically significant, I would probably still start off with monotherapy, see if I get my patients better, and if not, then proceed to combination treatment.

We see this all the time in the practice of medicine. I think Dr. Ballon would appreciate that we do not start off treating our patients with schizophrenia with our most effective drug. At least in this country, we don't start off with clozapine because of the side effect profile. We start off with other medications that have less side effects. And if and then they don't improve, then we go to something with a higher side effect burden.

This is the way I think about this. So even if it was unequivocally advantageous, 5 points on the CAPS, I would still be hesitant about changing my practice guidelines. And I can't imagine that the VA, or any other algorithm out there, would recommend starting off a combination treatment, especially in a population that has not been shown to be treatment resistant.

I think this speaks to the fact that FDA approval and an FDA label means something to clinicians and patients. It instills confidence that the evidence for these things is not

equivocal, but that we have confidence that these things work. And primarily, because 061 is questionable, I don't think it meets that level of evidence and confidence. And I think we should endeavor to maintain that for FDA labels and approvals because this is what our patients and our clinicians depend on.

So I think it shouldn't be taken lightly that we approve things because there is one positive trial and some supportive evidence. I think it really should be convincing, especially if the benefits are not that large compared to what we have in terms of standard of care. Thank you.

DR. NARENDRAN: Now, I'll move to our virtual panel members. Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Jess Fiedorowicz, University of Ottawa. I also voted no. Clear plans for managing type 1 error are essential for an adequate and well-controlled study, and they were missing from Study 061. So brexpiprazole plus sertraline doesn't meet the agency's typically required two adequate and well-controlled studies

to meet that standard.

The agency ultimately will need to decide whether the lower bar of one positive study plus confirmatory evidence is justified. They gave some examples of when this might be considered such as in the cases of rare diseases or if there are really compelling or clear results. In the case of PTSD, as highlighted today, this certainly wouldn't be a rare disease. In fact, it's common and has a tremendous public health impact.

Our discussions, starting with the interpretation of Study 061, I think the robustness of that discussion argues against those results being interpreted as being compelling or clear in some way. Then, as Dr. Raskind noted, and I think was quite influential in later conversation, this treatment is still available without indication, so it's not like this is going to be mothballed as a result.

I also would support further study. I think there are some encouraging signs here. Obviously, 071, is glowingly positive, and I think there are a

lot of things to be encouraged about in 061 as well, but not crossing that bar, in my opinion.

DR. NARENDRAN: Thank you.

Dr. Raskind?

DR. RASKIND: Yes. I don't want to be repetitious, so I won't, but I do want to repeat one thing. And that is, if there is a tiebreaker, to use another sport analogy, I would strongly encourage the sponsors to include an adequate sub-sample of combat veterans with combat trauma PTSD. They may be pleasantly surprised.

DR. NARENDRAN: Thank you.

Dr. Shaw?

DR. SHAW: Hi. Pamela Shaw. I voted no, I think for many of the reasons that were already stated that I won't repeat. But I will say, for me, really -- and there was excellent discussion of speakers, I think, in total today across the board -- it's important to think about that risk-benefit balance and to have confidence, not just hope that it's there. So in lacking that confidence, I had to vote no. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thomas?

DR. THOMAS: Patrick Thomas, Baylor College of Medicine. I voted no, again, for a lot of the reasons that were previously stated. I just want to note that the FDA said there have been times when they've looked at phase 2 as helpful, but that it's more, say, in rare cases or indications where there's not much out there, which isn't the case here. But even in times when they've done that -- for example, there was approval of Relyvrio in 2022, which was based on positive phase 2 results but failed to show a significant difference in phase 3 trial, and was later removed from the market in 2024 -- that speaks to when there's need, it's very compelling.

I feel for the veterans and those who suffer from trauma who are looking for new tools. As others have stated, we need confidence, and the stamp of the FDA helps to provide that. But it has to mean something, and we have to be diligent about the standards for that. Those are my thoughts.

DR. NARENDRAN: Before we adjourn, any closing comments from the agency?

DR. FARCHIONE: This is Tiffany Farchione. I just want to thank everybody who is here today, thank the folks who gave public comments, and especially thank the folks who participated in the clinical trials. I realize that this is probably not the vote that the applicant had expected or hoped for but, again, like Dr. Ballon was saying, I think this was still very valuable information to have and can still help with clinical practice. So, again, thank you all for your discussion today and for your time, and I'll pass it back over to you, Raj.

Adjournment

DR. NARENDRAN: It sounds good. I echo those comments. Thanks again to the sponsor, and all the panel members, and the agency. You guys do incredible work. We really appreciate it, and we'll adjourn the meeting now. Thanks.

(Whereupon, at 3:54 p.m., the meeting was adjourned.)