FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC) MEETING

Afternoon Session

Wednesday, February 3, 2016

12:56 p.m. to 4:36 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

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

12:56 p.m.

Call to Order

Introduction of Committee

DR. PICKAR: Good afternoon. Before we go any further, I just want to remind everyone to please -- checking myself silence your phones, smartphones, or any other devices that you may have. I want to identify once again the FDA press contact, Sandy Walsh. She's not here just now, but she will be the press contact. As we begin this afternoon's session, we're going to reintroduce ourselves and go from there.

I'm David Pickar. I'm the acting chair of the Psychopharmacologic Drugs Advisory Committee, and I'll be chairing this meeting. I will now call the meeting to order. We're going to start with our colleagues at the FDA, with Dr. Temple, and we're going to go around the table introducing ourselves. Thank you.

DR. TEMPLE: Bob Temple, deputy director, ODE-1.

DR. MATHIS: Mitch Mathis, director of Psychiatry Products.

DR. FARCHIONE: Tiffany Farchione, deputy director of Psychiatry.

DR. GAYMON-DOOMES: Aeva Gaymon-Doomes, medical officer, DPP.

DR. CHEN: Wen-Hung Chen, acting team leader, clinical outcome assessments staff.

DR. NARENDRAN: Raj Narendran, University of Pittsburgh, psychiatrist.

DR. STEIN: Murray Stein, University of California, San Diego and the VA San Diego Healthcare System, psychiatrist.

DR. IONESCU: Dawn Ionescu, psychiatrist at Massachusetts General Hospital.

MS. BHATT: Kalyani Bhatt. I'm with the Division of Advisory Consultant Management.

DR. PICKAR: David Pickar, Johns Hopkins.

DR. GRIEGER: Tom Grieger, and I work as a psychiatrist in the Maryland state psychiatric system and professor of psychiatry at Uniformed Services.

DR. HIGGINS: Jennifer Higgins, acting consumer representative.

DR. COMPAGNI PORTIS: Natalie Compagni Portis, the patient representative.

DR. McMAHON: Francis McMahon, National Institute of Mental Health intramural research program.

DR. HINKIN: Charlie Hinkin, professor of psychiatry at UCLA School of Medicine and director of neuropsychological services at the West Los Angeles VA.

DR. DICKINSON: Dwight Dickinson. I'm a neuropsychologist at the NIMH intramural program

DR. CONLEY: And I'm Rob Conley, the acting industry representative. I work at Eli Lilly where I'm the head of late-phase neuroscience development.

DR. PICKAR: Thank you very much. To repeat what we talked about this morning, topics like we will be discussing today can often be charged that people have strong feelings. Our goal is that the meeting will be fair and open. It's a forum for

discussion of these issues and individuals should feel free to express their views without any reservation. Thus, a gentle reminder, everybody will be able to speak into the record only if recognized by the chairperson. We look forward to a very productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. That's quite important.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you very much.

Now, I'll pass to Kalyani Bhatt, who will read the Conflict of Interest Statement. Kalyani?

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special

government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of the committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

During the afternoon session, the committee will discuss new drug application 20447, supplement 006, for the effectiveness of vortioxetine for the treatment of cognitive dysfunction in MDD, submitted by Takeda Development Center Americas, Incorporated. This is a

particular matters meeting during which specific matters related to Takeda's vortioxetine will be discussed.

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

With respect to FDA's industry representative, we would like to disclose that Dr. Robert Conley is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Conley's role at this meeting is to represent industry in general and not any particular company. Dr. Conley is employed by Eli Lilly.

We would like to remind members and temporary voting members that if the discussions

involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. PICKAR: We will now proceed with Dr. Farchione and the FDA opening comments.

FDA Introductory Remarks - Tiffany Farchione

DR. FARCHIONE: Good afternoon, everyone. In this afternoon's committee meeting, we're going to be discussing Takeda and Lundbeck's supplemental new drug application for vortioxetine for the treatment of cognitive dysfunction associated with depression. The applicants are proposing to add language to their label describing clinical trials using vortioxetine in this context.

Now, part of their application is they're presenting data from one trial in which cognitive

measures were used as a secondary endpoint. That was the one that sort of spurred their drug development program, and then two additional trials, their pivotal phase 3 trials that were specifically designed to evaluate the effect of vortioxetine on some cognitive endpoint. Now, both of these trials, they did have statistically significant result on their primary endpoint. Their primary endpoints in each of the trials were different, but they were overlapping.

The question that we have at hand this afternoon, though, is this would be a novel claim. This is something that we haven't put in a label up until this point. And even though, after the discussion this morning, it sounds like everybody is in agreement on this, we have opened the door to the idea that cognitive dysfunction is a legitimate treatment target in major depressive disorder. But the question here this afternoon is whether or not the studies that were being reviewed as part of this application were appropriately designed to assess the proposed claim.

Now, with regards to the DSST, which is going to be a major focus of the discussion, the applicant asserts that it might not be -- it's not really necessarily specific for any particular cognitive domain but that it's highly sensitive for overall dysfunction and sensitive to change. And that's really going to be a major matter of review for the committee to focus on.

With that, I think that we can probably go directly into the sponsor's discussion so that they can present all of their data to you.

Industry Presentation - Jonathon Parker

DR. PARKER: Good afternoon. I'm Jonathon Parker, vice president for CNS global regulatory affairs at Takeda. And along with our partner Lundbeck, we're here today to discuss vortioxetine and describe its ability to treat cognitive dysfunction in patients suffering from major depressive disorder or MDD.

I'd like to thank FDA for this opportunity to discuss vortioxetine, and we appreciate the agency's openness to consider new treatment

paradigms for patients with depression.

Vortioxetine is indicated for the treatment of MDD, and it's currently approved in over 60 countries, including the U.S. and EU. With over 830,000 patient-years of exposure, vortioxetine has an established and well characterized safety profile in MDD. In the clinical studies, we'll present the adverse events and adverse event rates were consistent with those originally seen in the registration studies. In agreement with FDA, the safety of vortioxetine is not at issue, so we do not plan to discuss vortioxetine's safety further unless the committee has questions.

Today, we'll focus on vortioxetine's ability to treat cognitive dysfunction in the same MDD patient population for which it's already been approved. The data will demonstrate that vortioxetine produced consistent effects across multiple studies. Data on this beneficial effect is now included in the majority of its label worldwide.

So why did we investigate this effect?

Vortioxetine is not solely an SSRI nor an SNRI. In addition to SERT inhibition, vortioxetine targets several serotonin receptors at clinically relevant doses. This pharmacology translates to in vivo and in vitro data that support a positive impact in cognitive function. Additionally, in animal models, vortioxetine actually reversed cognitive deficits. This evidence supports the findings of the pivotal studies that we will discuss today.

As you consider our development program, it's important to remember that there are no drugs approved in this area and there's no published guidelines for this path in MDD. Indeed, the program that we had evolved with our knowledge of the field and increased as we learned more about vortioxetine's effect in cognitive dysfunction in MDD. We also tried to maximize what we could learn. So in doing so, we chose to have the primary endpoints for the two pivotal studies be slightly different.

This program also evolved with input from experts in the field. However, what remained

consistent was our desire to demonstrate efficacy in cognition in an MDD patient population at the approved antidepressant doses.

The primary clinical evidence for vortioxetine's positive effect on cognitive dysfunction in MDD comes from three large-scale clinical studies. First, we explored these effects by including measures of cognition as secondary endpoints in the ELDERLY study, a study that was part of vortioxetine's original NDA. Encouraged by what we saw, we then conducted two new pivotal studies, the FOCUS and the CONNECT studies. Importantly, both studies were positive. In fact, vortioxetine is the first drug to demonstrate this effect in two large-scale, placebo-controlled studies.

In all three studies, vortioxetine showed a consistent statistically significant benefit in treating depression. The data also demonstrated vortioxetine's benefit in improving cognitive dysfunction for patients with MDD. The studies utilized the MADRS to measure vortioxetine's

antidepressant effect and the Digit Symbol Substitution Test, or DSST, to measure change in cognitive functioning.

For the FOCUS study, the DSST was half of a composite primary endpoint, while the DSST was the sole primary endpoint in the CONNECT study. In both studies, the primary endpoint was statistically significant. As Dr. Farchione said, the FDA's in agreement with this point.

While focused on the successful clinical studies, we also pursued other lines of research to further confirm a meaningful effect. This included pharmacology studies that drew us to cognition from the beginning of this concept. It also included non-clinical data that support evidence of an effect not seen with other antidepressants. Additionally, supportive clinical studies such as the hypothesis-generating ELDERLY study and the Functional MRI study further demonstrated that we were on the right track.

Finally, we included within the CONNECT study, the last of the pivotal studies, two

functional endpoints that support a positive benefit in patients and support the DSST as an endpoint.

In summary, I'd like to highlight the following key points. First and foremost, vortioxetine is a proven antidepressant. Second, cognitive dysfunction in MDD is an unmet medical need, and FDA has acknowledged that cognition may be a legitimate target. Furthermore, multiple cognitive domains are impaired in MDD, and the DSST is sensitive to impairments in domains relevant to MDD. And finally, the vortioxetine clinical program demonstrated a beneficial effect in cognition as assessed by the DSST in the acute MDD patient population.

This information is important for prescribers to be aware of in the care of their patients, and it should be reflected vortioxetine's product information. Therefore, we are proposing to add data to the U.S. package insert showing an effect in the current approved indication -- in the currently indicated population compared to placebo

on aspects of cognition assessed by the DSST. The exact wording and format will of course be subject to FDA discussions later, but this was the intent of our submission.

Before concluding, let me note that the following experts are with us here today to answer any questions you may have, and unfortunately, Dr. Goodwin was not able to make the trip today. So after this introduction, Dr. Jaeger will discuss how neuropsychological tests measure cognitive function and more specifically talk about the DSST.

After that, Dr. Olsen will describe the design and the results of our clinical studies. And we've asked Dr. Fava to provide his clinical perspectives regarding vortioxetine in the treatment of cognitive dysfunction for patients with MDD. And finally, Dr. Mini will provide our conclusions about the importance of having this information available to prescribers.

Now, it's my pleasure to introduce Dr. Jaeger, who will discuss the outcome measures we used in the clinical studies.

Industry Presentation – Judith Jaeger

DR. JAEGER: Good afternoon. I'm a clinical neuropsychologist, and my research work, over more than 25 years, has focused on characterizing the nature, course, and disabling consequences of cognitive dysfunction in a range of conditions, including MDD. Here are my disclosures.

I'll be making three main points today. First, that objective measures are necessary for clinical trials of cognition in MDD. Subjective ratings of cognitive dysfunction bring an important perspective. But since they may be influenced by depressed mood, subjective measures often disagree with objective performance.

Second, to serve as this objective measure, the DSST is appropriate and adequate in the clinical trial setting for several reasons: its reliability, stability, sensitivity to change, and sensitivity to the cognitive deficits seen in MDD. And finally, that change in performance on the DSST corresponds to clinically meaningful change in cognition.

Neuropsychological tests yield objective measures of performance, such as accuracy or speed on a task. Typically, they're designed to be narrowly sensitive to dysfunction in particular cognitive domains. However, no single test is a pure measure of a single cognitive domain. All are at least partly polyfactorial. Consequently, when used for diagnostic purposes, a battery of such tests is necessary to reveal a profile of cognitive strengths and deficiencies relative to norms.

Two points bear special mention. First -- and this is important -- virtually none of the standard neuropsychological tests in clinical diagnostic use were designed or validated to be sensitive to change over time as is required for clinical trials. Second, a test that has demonstrated sensitivity to change over time and is highly polyfactorial may be very useful in the context of clinical trials.

What makes a good test of cognitive change in the clinical trial setting? Well, first off, the measurement properties essential to a good

diagnostic test are different from the properties required for a test whose purpose is principally the measurement of change. The focus of a diagnostic test is on abnormality. Ceiling effects are not a problem because once we know performance is unimpaired, finer distinctions above normal are not important.

But when you measure change, such as in a treatment trial, essential features include normality, minimal floor and ceiling effects, high stability, and test/retest reliability, and brevity is essential to minimize fatigue and improve motivation. Since treatment trials rarely seek to tease out focal effects, a brief polyfactorial test may be an adequate and sufficient alternative to a long battery of more domain-specific measures.

There is one widely used traditional neuropsychological test that possesses many of the properties required for a test of change, and that is the Digit Symbol Substitution Test. In the DSST, the patient is instructed to copy a symbol into the blank below the numeral with which it is

paired. A time limit is set, usually 90 or 120 seconds, depending upon the version used, and the score is the number of correct responses in that time.

Since its widespread use beginning between the world wars, the DSST has proven to be the single most sensitive measure on the Wechsler scales to the presence of cognitive deficits seen in brain damage. But while it is extremely sensitive to the presence of brain damage, it is not informative as to its characteristics or cause. In this respect, it is sensitive but not specific.

As I've said, the DSST is an appropriate assay for detecting cognitive change. It is a polyfactorial test, meaning it is sensitive to multiple domains. Impairment or change on the DSST can occur as a result of a change in any of the domains involved. And in a clinical setting, further testing would be required to understand which domain.

Considered neuropsychologically, MDD is a non-focal condition in which disease impact on a

single domain is not of clinical interest or importance. Hence, the DSST is an adequate and sufficient measure of dysfunction and change.

So what does the DSST measure? Though it is often asserted that it measures processing speed, research makes clear that good performance on the DSST requires intact functioning in a range of domains, including those highlighted here. Ultimately, the brain solves problems through distributed networks, so no test is a pure assay of a singular cognitive construct. It makes more sense, then, to think about which cognitive functions must be intact to perform a test.

In clinical populations, DSST performance correlates highly with domains that do not involve processing speed, including attention and executive functions such as working memory, the same domains that are affected in depression.

Over its more than 75 years when the DSST has been included in extensive batteries, it has correlated highly with their composite scores with those correlations often exceeding 0.8. In this

recent factor analytic study of the MCCB in schizophrenia, you can see in the right most column that the DSST correlated highly and to an effectively equivalent degree with all three factors observed. And it's worth nothing that factor 1 contains two measures of executive functioning, while factor 3 is made up of measures that are not timed. These findings confirm that DSST operates as a polyfactorial test.

Turning now to my final point, one of the questions you're asked to address today is whether the changes seen in DSST are adequate evidence of clinically meaningful change. I'd like to offer some data, which help us understand the relevance of changes in DSST. First, I will demonstrate the relationship of DSST to disability outcome in MDD, and then I will discuss the use of benchmarking to help us understand how to interpret cognitive change in general, and then specifically with respect to the DSST.

Here are the results of a study we undertook to understand the role of cognitive dysfunction on

functional disability in MDD. We looked at the real-world functioning of patients 6 months after hospitalization for an acute episode of MDD. To do this, my colleagues and I developed a global index of disability called the Multidimensional Scale of Independent Functioning or MSIF.

To the left, you see that a rating of 1 reflects normal functioning, whereas a 7 reflects total disability in three main areas of life: work, school, and independent living. At 6 months, 45 percent of the patients sampled were still significantly to totally disabled. And when we gave these patients a battery of tests, we saw that cognitive dysfunction measured at the same time point was highly correlated with dysfunctional disability.

Notably, the DSST was among the most highly correlated tests to the disability rating. In fact, the DSST had an odds ratio of nearly 20, which was highly significant even after multiplicity correction. This is a standardized value, so in simple terms, it means that 1 standard

deviation on the DSST translates to a 20-fold difference of an MSIF rating higher or lower by 1 point.

Let's look a bit deeper at clinical meaningfulness by asking what a 1 point difference on the MSIF might mean for a patient's ability to function in real life. Here's someone with a rating of 4. Now change that by 1 point for the worse to rating of 5. What's likely is a life-changing outcome, potentially even the loss of a job. On the other hand, a patient with rating of 5 who moves to a 4 may be able to keep that job.

Of course, this was a cross-sectional study, but nevertheless, the relationship we found between the DSST and MSIF was so large that even a quarter of a standard deviation difference in DSST performance more than doubles the odds of a 1 point difference in life functioning, and a half of standard deviation difference yields 4 and half-fold difference in odds. The point is clear, if this were you or a loved one, even a modest difference in cognition as measured by DSST, for

better or worse, would significantly impact your life.

What is the magnitude of cognitive dysfunction in depression as measured with the DSST? Meta-analytic studies have shown that the average standardized effect size of cognitive dysfunction across a range of domains in MDD is about a half a standard deviation.

Looking at just the DSST, Snyder's meta-analysis showed a statistically significant difference between depressed and healthy individuals, with an effect size of 0.55. Of course, that's an average. Some do better and some worse. Recall that a half a standard deviation difference on the DSST increased the likelihood of a 1 point change on MSIF by about 4 and a half-fold in the model I just described.

Another way to understand clinical meaningfulness is to compare a given magnitude of effect with that observed under other well understood conditions. Benchmarking gives us a frame of reference for what various effect sizes

might mean for a person suffering from cognitive dysfunction in MDD.

In the case of alcohol, the clinical significance of its effect is societally accepted. We have laws that regulate driving while under its effect. In a similar way, the use of benzodiazepines and diphenhydramine, or Benadryl, likewise are often restricted for workers such as pilots and truck drivers, where public safety is at stake.

Note that the effect sizes for these compounds at the relevant doses tested range from approximately 0.27 to 0.68. Interestingly, the magnitude of chronic cognitive deficit experienced daily by people suffering MDD is in the same range as that seen acutely with alcohol intoxication or lorazepam use.

Now, of course this approach has limitations. Obviously, there are many differences between being intoxicated and having chronic depression. Benchmarking does however offer us a frame of reference for appreciating the magnitude

of impact on cognition of known CNS perturbations and provides us with an anchor to better understand the impact of MDD on cognition.

The DSST's sensitivity is not limited to change for the worse. For instance, it has been used to track cognitive improvement seen during withdrawal from alcohol and benzodiazepine dependence. So how can one 90-second test be this useful? Is it sufficient to measure cognitive change using only this test? Clearly, I think the conclusion is yes, and for the following reasons.

First, the DSST paradigm is robustly reliable. Longer batteries add burden and yet are not necessarily more informative. As we saw, the DSST is highly correlated with much longer batteries.

Next, the DSST is a powerful discriminator of CNS change and dysfunction. Further, the magnitude of deficit in MDD seen on this one test is comparable to that seen with much longer batteries. Finally, performance on this one test is robustly correlated with functional disability

in MDD. Hence, the DSST is sufficient to measure cognitive change, and a change on the DSST is clinically meaningful.

I would like to introduce Dr. Christina Olsen from Lundbeck.

Industry Presentation – Christina Olsen

DR. OLSEN: Good afternoon. I'm Christina Olsen, clinical lead for the cognition development program for vortioxetine. I'll begin by telling you why and how we chose to address cognitive dysfunction in depression. After that, I will share with you an overview of the design and methodology of our clinical studies. I'll then move on to the results of those studies and finish by summarizing the evidence.

It is vortioxetine's pharmacological profile that drove our decision to track the cognitive dysfunction in depression. Distinct from all our antidepressants, vortioxetine acts directly on a range of serotonin receptors as well as by blocking the serotonin transporter, as illustrated here. By acting on those serotonin receptors, vortioxetine

modulates a range of neurotransmittter systems that are key regulators of cognitive processing, including the gluatmatergic and gabaergic.

As you can see in our briefing book, we have shown that vortioxetine, unlike the SSRIs and the SNRIs tested, reverses cognitive deficits in a range of animal models, suggesting that indeed vortioxetine is different from other antidepressants.

While we were designing a depression study in an elderly population as part of vortioxetine's original NDA, Raskin and colleagues published a study on duloxetine, an SNRI, looking at this compound's effects on cognition in elderly depressed patients. Out of 4 tests, only the learning and memory paradigm showed significant effect versus placebo. Duloxetine did not improve performance versus placebo on tasks demanding more executive functioning. This included a simple coding task equivalent to the DSST.

Our preclinical findings on vortioxetine and the Raskin study prompted us to explore the effect

of vortioxetine on cognitive performance. To do this, we included prespecified additional endpoints in our ELDERLY study, two tests that were equivalent to those in Raskin. Then with a positive signal in ELDERLY, we decided to conduct two large scale pivotal studies in adults, FOCUS and CONNECT. For these, our primary aim was to confirm that vortioxetine's effect on cognitive dysfunction extended to the broader adult MDD population.

As the clinical program evolved, we also continued to expand the non-clinical and translational data. We did all this to better characterize the clinical profile of vortioxetine as an antidepressant with a beneficial impact on cognitive dysfunction in patients with acute MDD.

Let me turn now to an overview of the study design of our clinical trials. All three studies were 8-week placebo-controlled studies enrolling moderately to severely depressed patients. The baseline demographics for these studies were essentially the same as in the rest of our

depression program. This allowed us to evaluate vortioxetine's effect on cognitive dysfunction in addition to its antidepressant efficacy. While depression was a primary endpoint in ELDERLY, cognitive dysfunction was the primary endpoint in FOCUS and CONNECT. All doses were in our indicated range of 5 to 20 milligrams, and all three studies were globally conducted.

Finally, in ELDERLY and then again CONNECT, we chose duloxetine as an active reference. We did this primarily for assay sensitivity to verify antidepressant efficacy. We also considered duloxetine to be a high bar in addressing cognitive dysfunction due to its effect on learning and memory shown by Raskin.

We aimed in our pivotal studies to include a population that was typical for MDD trials, so we excluded, as we had in our initial NDA studies, other conditions, medications, and therapies that could have a CNS effect that might influence the cognitive assessments and treatment effect.

The two pivotal studies were very similar in

design and intent. Both aimed to confirm vortioxetine's effect on cognitive dysfunction in the broader adult MDD population, and both used a combination of objective and subjective measures as endpoints. There were, however, some differences in design, mainly to answer study specific questions.

We designed FOCUS to confirm the effect we saw in ELDERLY. We also investigated early treatment effects on cognitive performance. We designed CONNECT to ensure replication of FOCUS as well as replicating the distinct profile we saw in ELDERLY that had not been seen with the active reference. Finally, in CONNECT, we aimed at supporting clinical relevance by including assessments of functionality.

As a depression study, the primary endpoint of ELDERLY was Hamilton Depression Scale score. In FOCUS, we used both the DSST and RAVLT to generate a composite Z-score as a primary endpoint. This was guided by the effect we saw in ELDERLY. In CONNECT, we aimed at further characterizing the

distinct effect of vortioxetine on the DSST as an integrated major of cognitive function. To do this, we chose the DSST as the sole primary endpoint.

You see here the key secondary multiplicity controlled endpoints percentage in an hierarchical order for all three studies. Importantly, in FOCUS, the DSST was the first multiplicity controlled endpoint.

We included a number of additional prespecified endpoints in each study as supportive evidence. Comments for all three studies, the MADRS and the CGI-I, were included to address depressive symptoms as well as clinical global impression. We added a range of objective and subjective endpoints to support our primary cognition endpoints.

As presented in the briefing book, we used different methodologies in our pivotal studies according to the number of assessments post-baseline. In FOCUS, we applied MMRM. In CONNECT, we used ANCOVA LOCF. In both FOCUS and

CONNECT, the path analysis was also prespecified.

Across the three studies, the results of the analysis of primary and key secondary endpoints were under full multiplicity control for vortioxetine in a prespecified test order hierarchy.

Additionally in FOCUS, we applied a Bonferroni adjustment for multiple doses. As I present results, you will see statistical significance indicated by stars. Additional endpoints for vortioxetine as well as results for the active reference are presented with nominal p-values, and you will see nominal significance indicated by daggers.

Let me now give you an overview of all the measures of cognitive function, functional capacity, and work limitations we used across our studies. As you can see, we prioritized objective neuropsychological tests for the reason outlined by Dr. Jaeger. In FOCUS and CONNECT, we included a number of neuropsychological tests adequate to address the broad range of cognitive domains

relevant for MDD.

We also chose to capture patients' perception by adding subjective measures of cognitive function. And in CONNECT, in order to assess whether vortioxetine's beneficial profile would translate into improved functioning, we extended the number of measures. We included a functional capacity measure and a work productivity measure. We used well known validated tests sensitive to cognitive functions known to be impaired within depression. Yet, at the same time, we were mindful of study and patient burden.

Let me underline that vortioxetine improved depressive symptoms across all three studies. Likewise, in the studies in which it was included, duloxetine also improved depressive symptoms, thereby validating the assay sensitivity of the studies.

As I turn now to ELDERLY, let me start by saying that it met its primary endpoint significantly improving depressive symptoms. In ELDERLY, both vortioxetine and duloxetine improved

performance versus placebo on the RAVLT, the learning and memory tasks. Yet, while both compounds were effective in improving depressive symptoms, only vortioxetine had a positive effect on the DSST.

These results supported our hypothesis that vortioxetine has an effect on a broad range of cognitive domains relevant to MDD not limited to learning and memory. It also replicated the Raskin findings that duloxetine works on learning and memory as assessed by the RAVLT but not in the domains needed to perform on the DSST. Finally, ELDERLY demonstrated that you would not necessarily see an improvement in your cognitive performance on the DSST when you have an improvement in your depressive symptoms.

Let me turn now to our FOCUS pivotal study. Both doses of vortioxetine met the primary endpoint by significantly improving patients' cognitive performance as assessed by the composite Z-score comprised of DSST and RAVLT. As you see here on the Y-axis to the right, we are also presenting our

results as standardized effect sizes versus placebo. And to put the magnitude of these effect sizes in the context of the effect on depressive symptoms, they were comparable to the ones we saw on the MADRS. Considering the level of effect sizes of approved therapeutics in psychiatry, these effect sizes were relatively large.

In addition, you can see that the first key secondary endpoint that DSST considered on its own was significant for both doses, confirming that the effect we saw in ELDERLY held true for adults with MDD. The testing hierarchy stopped there as indicated by the p-value for the learning score of more than 0.025. After that, although the p-values were low for the memory scores supporting that vortioxetine has effect on learning and memory in the adult population, they were nominal.

You see here that vortioxetine improved cognitive performance versus placebo across all the neuropsychological tests included in FOCUS and with clinically relevant effect sizes. These findings substantiate the effect of vortioxetine on the

DSST. They also support that vortioxetine's effect is not limited to specific cognitive domain but extends across a broad range of cognitive functions. Please note that a large effect size was seen for the DSST, thus reinforcing its sensitivity as a measure of change.

Let me conclude this review of the results from FOCUS with the PDQ total score, which captures subjective patient-reported cognitive function. The PDQ, for example, asks patients to report how often they have trouble concentrating or making decisions. As you see, both doses of vortioxetine improved cognitive function as perceived by the patients themselves.

Let's move on now to the CONNECT study. In CONNECT, vortioxetine significantly improved DSST performance versus placebo. As I mentioned earlier, we included an active reference in CONNECT as we had in ELDERLY. We wanted to be confident that the improvement in cognitive performance was not just representative of an antidepressant effect.

Recall that both vortioxetine and duloxetine improved depressive symptoms. As you see, duloxetine, despite improving depressive symptoms, did not separate from placebo on the DSST. Although the numerical differences between vortioxetine and the active reference were not as clear as in ELDERLY, CONNECT substantiated that vortioxetine's cognitive effect on the DSST was specific to vortioxetine. Vortioxetine also met significance for both key secondary endpoints, the PDQ and the CGI-I. As you can see, this was also true for the active reference.

Both vortioxetine and duloxetine improved patients' depressive symptoms, so we need to consider that such improvement may confound the interpretation of the treatment effects on cognitive dysfunction. Specifically, subjective measures may to a last degree reflect a patient's mood state. In other words, while subjective measures do provide clinically meaningful information, objective measures, especially in the clinical trial settings, help us to disentangle

effects on cognitive function from effects on general depressive symptoms.

This graph shows vortioxetine's effect on the primary endpoint, the DSST, and then to the right, the additional prespecified neuropsychological tests. We did not see in CONNECT the same robust effect across all neuropsychological tests as we had in FOCUS. Please note, though, that effect sizes in CONNECT were lower across the board than they were in FOCUS, including the effect on mood.

Importantly, while not reaching nominal significance, the pattern was in favor of vortioxetine relative to placebo except for the Stroop test, supporting vortioxetine's effect on cognitive dysfunction as assessed by the DSST.

Finally, in addition to the DSST, the other test where vortioxetine separated from placebo was the Trailmaking B test in more executive function demanding tasks. Importantly, this replicated the positive finding on the Trailmaking B already shown in FOCUS.

As in FOCUS, we also looked at a composite score in CONNECT, with difference that in CONNECT we included a composite Z-score comprised of all the neuropsychological tests. Although this information is not in the briefing book, I would like to share it with you. Note that vortioxetine improved cognitive performance as assessed by the overall composite score and that this improvement was nominally significant unlike duloxetine. Further, the effect size of this improvement was comparable to the effect size on the DSST.

To address the question of whether vortioxetine's distinct profile would translate into improved functioning, in CONNECT we included the UPSA as an objective measure that correlates to everyday functioning. Patients are asked to role play daily life related tasks in order to evaluate their skills in a range of errors. For example, patients are asked to dial a number from memory or call to reschedule a doctor's appointment.

The UPSA has been widely used, particularly

but not limited to schizophrenia trials, but the CONNECT study was the first large scale depression study in which it has been applied. This graph shows that vortioxetine did indeed improve patients' functional capacity as measured by the UPSA, while the active reference did not. This suggests that performance-based measures such as the UPSA capture effects not addressed by the traditional depression scale such as the MADRS.

Work related outcomes are important functional outcomes for depressed patients, so we also included the WLQ in CONNECT as a way to assess effects on real-world functioning. The WLQ is a work limitation questionnaire, which we ask all working patients in the trial to fill out. We ask patients to rate how difficult they found it to start work each day or to work the required number of hours as reflected by the time management score. Likewise, they rated how difficult it was to work fast enough or to handle the workload as reflected by the &output demand score.

You can see vortioxetine, in contrast to the

active reference, separated from placebo on the time management score. This suggests that the WLQ captured effects related to functioning that cannot solely be explained by the improvement in depressive symptoms. As with the UPSA data, we were intrigued by these findings, as they added to the evidence of clinical relevance in supporting the distinct profile of vortioxetine.

Let me summarize our evidence. Vortioxetine consistently improved DSST performance across all three studies with standardized effect sizes ranging from 0.25 to 0.52. FOCUS confirms that the effect we saw in ELDERLY held true for adults. CONNECT replicated the findings from FOCUS. As you heard from Dr. Jaeger, such effect sizes are similar in magnitude to the cognitive deficits seen in depression. They are also similar to all benchmarks and they want to be considered as clinically meaningful.

In the studies where it was included, the active reference did not reach significance despite improvement on depressive symptoms, supporting that

these effects cannot be attributed solely to the effects on depressive symptoms.

Indeed, we aimed throughout our clinical program to support that vortioxetine's effect on cognitive dysfunction in MDD was not just due to improvement in mood. To do this, we did two things. First, in two of our studies, we used an active reference with reliable effects on mood. Second, as you see here, we also applied a path or mediation analysis in all three studies, prespecified in FOCUS and CONNECT.

Simply put, this statistical analysis gives us an estimate of the proportion of indirect effect that is mediated through improvement in depressive symptoms. This is illustrated by the white part of the bars. It therefore also gives us an estimate of the proportion of effect on cognitive dysfunction that cannot be explained by improvement in depressive symptoms, as illustrated by the colored part of the bars.

Across all three studies, when you adjust for the effect on the MADRS, the majority of the

effect of vortioxetine on DSST is retained, thus indicating a notable independent effect on cognitive performance. Let me note that the effect of duloxetine was primarily an indirect effect mediated by the effect on depressive symptoms.

Taken together, our nonclinical and our clinical data suggests that vortioxetine's effect on cognitive dysfunction in MDD is both distinct and mood-independent. We have a substantial number of animal studies that support vortioxetine's beneficial effect on cognitive function not seen with SSRIs or SNRIs, suggesting that vortioxetine is different from other antidepressants.

Recent data from our human fMRI study in subjects remitted from depression suggests that vortioxetine improves neuronal efficiency during cognitive processes. You will find all these data in our briefing book.

Most importantly, the data from all three of our clinical studies demonstrated a positive and lasting mood-independent effect on cognitive dysfunction as measured by the DSST, and we saw

this effect substantiated across a broad range of cognitive functions, a profile not seen with an active reference. Finally, these effects are further supported by improvement on measures of performance-based functional capacity, work productivity, as well as on patient-reported cognitive function.

Thank you very much, and now Dr. Fava will share his clinical perspective on the data.

Industry Presentation – Maurizio Fava

DR. FAVA: Thank you very much.

Good afternoon. I'm Maurizio Fava, and I'm executive vice chair of the Department of Psychiatry at Mass General. I'm also director of the Division of Clinical Research of the MGH Research Institute.

I'm a practicing clinician, and I've been a depression researcher for 30 years. And I certainly have focused some of my research on the effects of depression on cognition and the effects of treatment on cognition in depression. I have served as a consultant to Takeda and Lundbeck for

the past few years. I do all my consulting through Mass General, so I don't receive any personal compensation for my consulting, either directly or indirectly.

Now, this morning, before I begin, I have to say that the discussion really originated with me as a clinician, as I've had a number of cases of patients presented to me after responding to other depressant therapies and yet complaining of cognitive issues at their workplace.

They would tell me that they would go to meetings, and they wouldn't remember the words. They couldn't articulate their thoughts. They couldn't focus. They would get distracted. And they felt that even though their mood was clearly better and their energy and their sleep, there was something still fundamentally wrong with their cognition. And I think as a clinician, it's very important that those patients have treatment options.

As we've heard this morning, cognitive dysfunction is a common symptom in depression, and

it is a significant contributor to functional impairment in these patients. As such, it's associated with a greater severity of illness and disability, and it's often unfortunately not adequately addressed by existing therapies, as shown very well by the recent review by Richard Keefe. In fact, I think this morning, Dr. Ionescu mentioned the use of stimulants, that sometimes clinicians add on to another depressant because of the inadequacy of addressing cognitive impairment in depression.

Many people in our field feel that cognitive impairment in depression is not as important as in schizophrenia or bipolar disorder, as Dr. Trivedi mentioned this morning. But we're I think finally beginning to see that that is not the case. So I've taken the opportunity of using data from the FOCUS and CONNECT studies to provide an example of how common cognitive dysfunction is in major depression. And as you can see from the next slide, cognitive dysfunction was quite common.

We've taken a very conservative approach to

the definition of objective impairment. So we've used as a definition 1 standard deviation or more below the norm on at least two of four objective tests, including the DSST. And using this definition, as you can see, approximately 65 percent of the patients in both CONNECT and FOCUS had cognitive impairment.

In CONNECT, when we add those, we're cognitively impaired by subjective measures only, and we use for that the CPFQ, this instrument that we've developed, where they scored markedly impaired on at least two of the four CPFQ cognitive domains. You can see that as many as 80 percent of the patients with depression report cognitive impairment. So this is a very common problem in clinical practice.

When you look at the data for vortioxetine on DSST, as a clinician, I'm struck by the fact that you have extraordinary consistency across the three studies. It's so hard in depression studies to have consistent outcomes. Half of the time, when we run studies, effective treatment separates

from placebo only half of the times. So the fact that both the ELDERLY, the FOCUS, and CONNECT was a consistent effect size I think is very impressive. I think in the cognitive measure, the effect of the cognitive measure is clearly unprecedented. In addition, this effect is largely independent of the mood effect as suggested by the path analysis that Dr. Olsen referred to.

Now, the starting point to answer the question of the clinical meaningfulness of this data I think is the magnitude of the standardized effect on the DSST, which range between 0.25 and 0.52 for vortioxetine, and it's in sharp contrast to the effect size as detected for duloxetine.

Second, from a patient perspective, it's important to note that the improvement and cognition of vortioxetine was not limited to objective measures but was also shown and demonstrated in the subjective measures, so cognitive impairment.

Third, the ultimate goal of treatment of cognitive dysfunction in depression is to actually

improve function. And therefore, the treatment effects of vortioxetine that were detected with the WLQ and with the UPSA are clearly noteworthy, as they speak to this effect on functional capacity. And last but not least, there were no deleterious effects of vortioxetine treatment on other measures of cognitive dysfunction.

So I'm here today, as a clinician and a clinical researcher, to give you my perspective on this data, and my knowledge of this data clearly affected my practice. Recently, I had a patient in my practice, who had been on an SSRI for some time, doing well, and I switched him to vortioxetine.

A couple weeks ago, he came back for follow-up, and he said to me, "You know, Doctor, on the SSRI, I thought I was better, and I was. But upon switching to this new antidepressant, I feel the same mood-wise, but my thinking has clearly improved, my memory is better, and my mind is sharper." And he asked me, "Am I imagining this?"

Well, I think this is an important factor, that my knowledge of the data from the studies led

me to prescribe in this case a different treatment, and this data, in my opinion, should be available to a wide range of clinicians. Cognitive dysfunction in depression is an important clinical problem for virtue of its prevalence, persistence, and impact on overall function. Vortioxetine has demonstrated favorable treatment effects on cognition in MDD across these studies.

In the three studies in which the effects were shown to be largely independent of the effects on mood in contrast to duloxetine, as pointed out by Dr. Olsen. Moreover, vortioxetine treatment was also associated with improved subjective cognitive function and improved functional capacity.

These results in my mind are clinically meaningful with respect to the treatment of depression. And I feel that they should be shared with physicians treating patients with depression, particularly in the context of something that Dr. Ionescu alluded to this morning. There are many clinicians that end up using polypharmacy just adding Modafinil and stimulants with very little

data. But they do it because there's an unmet need. And they end up using these drugs and using polypharmacy to address the fact that many patients respond to antidepressants but still have cognitive impairment.

Knowing that monotherapy with vortioxetine may reduce the need for polypharmacy down the road in my opinion is important, and knowing that there is an effect of vortioxetine consistently through different studies I think is also important. Thank you.

So I'd like to ask Dr. Mini, who's vice president and global medical head of CNS medical affairs at Takeda, to provide a conclusion.

Industry Presentation – Louis Mini

DR. MINI: Good afternoon. My name is Lou Mini, and I'm global medical head for neuroscience at Takeda Medical Affairs. I'm a board certified psychiatrist who was practice for several years, and it's now my privilege to deliver the conclusions of today's presentation.

Up until this point in time, the

effectiveness of pharmacologic treatments for major depressive disorder has largely been equated with reducing mood and somatic symptoms to some acceptable level. This is what most of us clinicians were taught during our training. You just heard Dr. Fava describe how cognitive dysfunction affects a large percentage of patients with major depression.

As was mentioned this morning, we've known this for a long time, yet this important aspect of the illness has not been well addressed, and as such represents a significant research and treatment gap since cognitive dysfunction is a serious and disabling feature of major depressive disorder for many patients.

Dr. Olsen presented the data related to the vortioxetine cognition program in depression, the results of which represent important new medical information that we believe should be added to the U.S. product label for vortioxetine. This is needed in order to enable the medical community to more fully treat patients with MDD by understanding

better in addressing its cognitive component.

There's also a need to better understand the medications used to treat patients with depression, and that was the purpose behind these clinical trials and why we examine vortioxetine in this way and to this extent.

An antidepressant therapy that can improve cognitive dysfunction would provide an added benefit by broadening a clinician's ability to treat and address this key aspect of major depressive disorder, thus helping many patients suffering with this illness. The treatment of major depression should not be focused only on mood and somatic symptoms, but should also target cognitive symptoms in order to offer patients the best chance at optimal recovery.

The vortioxetine cognition program was innovative and founded on a sound scientific rationale, strong research principles, and supporting evidence from a variety of sources. There are four key points that argue for benefit, and I'll take them one at a time.

First, the pharmacologic profile. As you heard, vortioxetine serotonergic receptor activity is believed responsible both for its antidepressant properties and its effect on cognitive dysfunction.

Second, nonclinical studies show a consistent reversal of cognitive deficits in animal models. This was not seen with SSRIs and SNRIs subjected to the very same testing.

Third, clinical fMRI data in remitted patients displayed effects in key brain regions when performing a cognitive tasks after vortioxetine administration, effects that are in direct opposition to what you see in major depressive disorder.

Finally, prospective placebo-controlled clinical trials. These trials were notable in their size, scope, and focus and are aimed directly at assessing vortioxetine's effect on cognitive dysfunction in adult patients with acute major depressive disorder. So at a molecular level, a preclinical level, and an experimental medicine level, you can see the scientific rationale built

with the most important data being the effects seen on the DSST versus placebo in clinical trials with vortioxetine.

This was the first clinical program to specifically address the unmet need of cognitive dysfunction in adult patients with acute major depressive disorder, and as such, there was no roadmap, no guidance on clinical research to follow. As was mentioned, this has been an evolving clinical concept.

A commitment was made by our companies to learn more about vortioxetine's treatment effects in depressed patients. Our research was grounded in the best science available, and we consulted with a variety of leaders in the field, both with respect to cognitive in depression and neuropsychological testing.

The two pivotal trials, FOCUS and CONNECT, each involving over 600 patients, went well beyond any prior clinical research on this issue with any other antidepressant, and these clinical trials achieved their main objective. The primary

endpoint was met in both pivotal trials.

To conclude, vortioxetine is indicated for the treatment of major depressive disorder. In two large adequate and well controlled studies, vortioxetine was effective in the treatment of cognitive dysfunction and acute major depressive disorder as assessed by the DSST. And as experts Dr. Jaeger and Dr. Fava described earlier, these data are clinically meaningful. Moreover, the results are consistent and advance our understanding of vortioxetine's clinical profile.

It is the sponsor's view that this is important information to communicate to prescribers through the product label. We propose adding such information in the clinical study section language that describes the effect of vortioxetine versus placebo on the DSST within the currently indicated population of patients with major depressive disorder and language that appropriately conveys the meaning of these results.

On behalf of the entire team, thank you for the opportunity to present what we believe is

important research that warrants consideration.

Clarifying Questions

DR. PICKAR: Thank you very much. We're going to move to some clarifying questions before break, and then FDA presentation. The floor is opened to questions of individuals. It will be helpful to ask them to specific individuals or whatever seems appropriate. Dr. Grieger, did you have a question? Oh, sorry. See, I didn't look at my list here.

Yes, Dawn?

DR. IONESCU: Thanks so much. I'm not sure who to direct this question to, but in both the FOCUS and CONNECT studies, the objective impairment was somewhere around 64, a little bit more, in both of the studies for the patients. Is there any indication that the DSST scores improved more in the patients who came in with baseline cognitive dysfunction versus patients that weren't considered to have cognitive dysfunction as according to the subjective impairment scale to begin that study?

DR. MINI: I'm going to direct your question

to our clinical lead, Dr. Olsen.

DR. OLSEN: Thank you. The short answer is no. There were no subgroup identified with a particular beneficial effect of vortioxetine. Across the three studies, you also actually had a benefit, you can say, in higher performance patients. And just to remind you, we do not know the premorbid level of the performance.

DR. PICKAR: Dr. Grieger?

DR. GRIEGER: Just to put this into perspective, what are the range of the raw scores on the DSST? Would it be the actual number of questions answered prior to treatment, post-treatment? Are we talking about a change that goes from 42 to 48? Are we talking about a change that goes from 42 to 44?

DR. MINI: Dr. Olsen again.

DR. OLSEN: It is more in the range of 42 to 48 to 50.

DR. GRIEGER: Do you have a graphic that shows that?

DR. OLSEN: Yes.

DR. GRIEGER: Because the other question I have that goes along with that is, are there some responders -- some number of subjects who improve dramatically that they pulled the statistic up, whereas a large portion may not improved at all? That's why -- a lot of the graphics don't show that.

DR. OLSEN: Yes. You're thinking about the distribution curve, some changes.

DR. GRIEGER: Essentially, yes, but also the raw score. We're talking about clinical significance. How helpful is it to go a couple of points up on that test?

DR. OLSEN: I will ask my colleagues to comment on that.

DR. MINI: So you're asking what's the significance of the change that we saw in the study? I just want to clarify so we get you the right answer and the right person.

DR. GRIEGER: I want a perspective on this. I want to know -- you know, like you would have MADRS score or a HAMD score. What is the score

change associated with the effect size? Raw data.

DR. MINI: Okay.

MR. LOFT: Henrik Loft from Lundbeck, biostatistics. Concerning the baselines, in all three studies, they were around 42. I'd like to show the distribution of the changes from baseline in the FOCUS study. Slide up, please.

You'll note, scores to the right are improvements. And as you can see, in neither of the groups are tendencies for spikes to the left, that would indicate that the results were driven by very large responses by a few subjects or by many subjects. All three distributions also show nice normality and no evidence of -- by modalities. And you can see the ranges of the changes from minus 20 to plus 20.

DR. GRIEGER: So those are actually the score changes? Somebody correctly did 18 digits more after being treated?

MR. LOFT: Yes.

DR. GRIEGER: Okay. Thank you.

DR. PICKAR: Dr. Stein?

DR. STEIN: Question for Dr. Fava. I just want to -- I was impressed by the story you were telling about the patient you saw recently and the cognitive dysfunction that the patient had and how important that was. So knowing what you know about cognitive dysfunction in depression and what you've learned about this drug, how would you see -- and I'm asking you to extrapolate. How would a label change that's being proposed affect the way you would practice?

So if you had somebody who was doing really well on their -- let's say it's an SSRI, except you then detect that they've still got some residual cognitive complaints, would you actually switch medicines to a drug like vortioxetine or would you try and pick up cognitive symptoms before you started treatment and preferentially go with that drug? And if you were going to do that, how would you do that clinically?

DR. FAVA: Well, in practice, we do this all the time. For example, when a patient is better on an SSRI but the insomnia has not improved at all,

you will switch, let's say, mirtazapine, or tricyclic, or seek promoting [indiscernible] antidepressant to really kind of address this residual problem that is not resolved by the drug. So in practice, we do switch antidepressants when we feel that the antidepressant that they responded to has not addressed a particularly critical aspect of the depression.

Now, I don't know what should go on the label. I think this would be, assuming negotiation, part of the negotiation. But it seems to me that as a clinician, I would like to be able to know the data, and now simply know it because I'm an expert in this area and I've seen the data.

DR. PICKAR: Dr. Portis?

DR. COMPAGNI PORTIS: I have a few questions. One, just have a follow-up on Dr. Grieger's question. I understand that there's statistically significant numbers, but what were the actual numbers of people that were helped, that showed a distinct improvement?

DR. MINI: Well, are you talking about me or

responder analysis?

DR. COMPAGNI PORTIS: Yes.

DR. MINI: That's a key issue. We've looked at this in a number of ways, and I'll have Dr. Buller describe it for you.

DR. BULLER: Raimund Buller, clinical development, Lundbeck. We looked at response rates in different ways, so maybe the easiest one is to look at who and how many patients would have a 1-point, 3-point, 5-point improvement. You have seen the distribution. There are individuals there that have larger improvements. But the slide I'm going to show -- slide up -- just shows you, for the two studies, the percentage of patients who have at least 1 point or at least 5 points, that's the extremes.

You see across the range, there is up to 70 percent of patients who would have a benefit of 5 points or larger on vortioxetine and 20 percent less on placebo. This translates into number needed to treat of 5.

In the CONNECT study, as you have seen, the

effect sizes are somewhat larger, but even so, you have always an advantage, numerical advantage for vortioxetine over placebo.

DR. COMPAGNI PORTIS: And a couple other. And how do you explain -- in the material we got, there was a difference in the response rate, the U.S. population versus those that were studied in centers outside the U.S. So I wonder how you explain or understand that.

DR. MINI: Dr. Olsen?

DR. OLSEN: We did indeed see lower effect sizes in the U.S. population compared to the non-U.S. Now, that is unfortunate and not uncommon. That we had experienced in our overall depression program, to notice that this was not only for DSST, but that actually was for the whole range of efficacy assessments. The exact reason, we do not know. However, important, it was in the same direction, so we also improved performance in depression in this U.S. population.

DR. MINI: And I would further point out that that was not specific to vortioxetine. We

also saw the same thing with duloxetine as well.

DR. COMPAGNI PORTIS: How did you choose the duloxetine rather against an SSRI? I'll try to stop asking --

DR. MINI: Okay. Dr. Olsen?

DR. OLSEN: So we were intrigued by the study from Raskin, where they in fact had shown some effect on cognitive dysfunction, the learning and memory. And also, an SNRI have another profile than SSI [ph], so there's also contribution from the noradrenergic system. Now, vortioxetine has this unique broader profile, and our hypothesis was would we in fact act on a broader range of cognitive function unlike duloxetine. So, yes, we chose duloxetine as a high bar.

DR. COMPAGNI PORTIS: So just to clarify also, in the presentation, you said that there are lasting effects, cognitive positive effects, but the study was only 8 weeks. Is that correct? Do you have data beyond that?

DR. MINI: Both studies were of 8 weeks duration, that's correct. We don't have data

beyond 8 weeks on cognitive performance.

DR. PICKAR: Dr. Ionescu?

DR. IONESCU: I was wondering if you could elaborate a little bit more on the fMRI data? We learned about some interesting things this morning, specific areas of the brain that are believed to be affected in patients with depression and cognitive dysfunction. Were there any changes pre-, post-vortioxetine in these specific brain areas that could potentially be important?

DR. MINI: The fMRI study was, again, another piece of evidence to add to the scientific rationale. We'll have Dr. Connie Sanchez address your particular question on the study.

DR. SANCHEZ: Connie Sanchez, pharmacology, Lundbeck. I think the primary aim of this fMRI study was to investigate the effect of vortioxetine versus placebo under neuronal networks that are involved in the working memory tasks or the impact task. And what we found was that in the dorsal lateral prefrontal cortex, we saw a reduction of the bold signal in the group that was treated with

vortioxetine compared to placebo, which would indicate a reduced energy requirement in order to perform the tasks.

In addition, we saw a significant decrease in the hippocampus, a further deactivation of the hippocampus, which is another network effect that has been seen to be necessary for the impact task. So basically what we found was that vortioxetine decreased the energy demand to conduct a cognitive task.

DR. PICKAR: A couple questions here. Were there any predictors of individual response? As an old clinical researcher, I always like to see what got us there. Anything flagged on those folks?

DR. MINI: We looked at this in a variety of ways. We did not see anything that stood out. However, Dr. Buller could go over the subgroup analysis for you.

DR. BULLER: Yes. We were also interested in this question, and therefore we did the usual subgroup analysis by age, gender, region, and severity level. Slide up, please.

What you see on this slide is the forest plots for the effect of vortioxetine in the three studies by various subgroups. And what may make you wonder is the effect on age, about 50 in the CONNECT study on men. But please note that these are small numbers, so they don't really allow for a conclusion, and they are not replicated. Especially, it's worthwhile pointing out that in the ELDERLY study, we have shown efficacy. So in summary, we did not see any subgroup that had particularly better or worse efficacy in our trials.

DR. PICKAR: The DSST is maybe one of the most sensitive measures for just global dysfunction in general. And I'm sure you count -- I'm sure Maurizio in his practice encounters people who have processing speed deficits as part of clinical psychiatry, ranges of those.

My guess is there was no premorbid information about these people, if anybody had a learning disability, anything that would speak for why they may not have responded or did respond.

And secondarily, did you ever consider administering it to somebody with DSST deficits not related to depression?

DR. MINI: Dr. Olsen?

DR. OLSEN: To your answer, you were asking whether we had a specific premorbid level in any indications on the DSST. We had not. To your second question, please rephrase that again. Thanks.

DR. PICKAR: That was a principle, and then the next question would be, since it's quite common to have DSST scores in the range you're looking at, it's just not that uncommon, did you ever administer it to somebody with DSST scores like that but who was not depressed?

DR. OLSEN: No. In fact, in the imaging study where we also had a healthy control group, we did also administer vortioxetine. And they actually also administered the DSST, but there was no improvement on the DSST.

DR. PICKAR: Dr. Narendran?

DR. NARENDRAN: I just have a general

question. The DSST, has it been used for any other product development for any other clinical population like for psychostimulants in ADHD? If you use it, do you know what the effect size would potentially -- has it been -- is it known? Is it available? And how would that compare to your effect size in depression?

DR. MINI: I'm going to turn to our experts in the group. Dr. Jaeger maybe; Dr. Harvey may have comment after.

DR. NARENDRAN: Thank you.

DR. JAEGER: Yes. I just want to make a point here. It's extremely difficult to improve cognitive function in humans. It's very difficult to improve it, to move it at all, right? And in ADHD, the endpoint for clinical trials is a behavioral scale, not typically a cognitive test. So I'm not aware that it's been used in that way. It has been used as a highly sensitive measure for detecting adverse effects, so you'll see it used there as a safety measure in fact.

DR. MINI: Dr. Harvey, did you want to

add --

DR. PICKAR: Phil, Dr. Harvey, do you have anything to add?

DR. HARVEY: I'm Phil Harvey from the University of Miami, and I'm being compensated for serving as an expert on this panel, but I have no financial interest in the outcome in terms of stock at Takeda or Lundbeck.

The DSST in related measures like Trailmaking Part B have been used as outcome measures in computerized cognitive enhancement studies. And in one of the more successful ones of those, the effect size for improvement on Trails B was 0.4 standard deviations, which is exactly the magnitude of improvement seen with vortioxetine treatment on Trails B in these clinical trials.

So that's the level of improvement that can be induced with a systematic cognitive remediation intervention. Unfortunately, the majority of cognitive enhancement studies where the Digit Symbol has been applied, or related tests, have been unsuccessful because, as Dr. Jaeger said,

cognitive enhancement is difficult to come by pharmacologically.

DR. PICKAR: Thank you very much. We're going to be taking a break, a 10-minute break. Remember, no discussions except for -- Dr. Mathis?

DR. MATHIS: Thank you. I'll just ask one more question. Dr. Fava, on your slide CP-4, you define an objective impairment as more than 1 standard deviation below the norm on at least two of the following: DST, CRT, Trailmaking A or B. And I think that's a baseline that you have.

DR. FAVA: That is correct, yes, the baseline, correct.

DR. MATHIS: Do you or the company have those two bar graphs post-treatment for vortioxetine and duloxetine in CONNECT for instance, with placebo?

DR. FAVA: Let me ask Dr. Olsen.

DR. OLSEN: Yes, we do have. Slide up, please. So what we do see is that in the other graph, the FOCUS and CONNECT, it's the patients which have impairment in the cognitive tests, in

two or more cognitive tests more than 1 standard deviation below norms, and the lower figures are patients who did not. So in FOCUS, you will see that in both groups. You will see an improvement on your DSST. In CONNECT, the improvement on the DSST is more pronounced in the objective impaired patients.

DR. PICKAR: Sure.

DR. UNGER: Hi. I'm Dr. Ellis Unger. I'm director of Office of Drug Evaluation I. But the question was, really, in that slide, CP-4, you've basically defined objective impairment as at least 1 standard deviation below the norm on at least two of the following tests.

So the question is, post-treatment in CONNECT -- yes, talking about the bar graph on the left, and there's the definition at the bottom. So then, in CONNECT, for the three treatment groups, placebo, duloxetine, and vortioxetine, what would that bar graph look like post-treatment?

DR. OLSEN: All three?

DR. UNGER: Yes, all three. And you may not

have it now, but maybe you could get it.

DR. OLSEN: I have it now. Slide up, please. So you'll see the same graphs, and now to the right, also with duloxetine. Again, across all three, all the four groups, there's an improvement of vortioxetine on the DSST. You see it for the duloxetine active reference, also a more pronounced effect in the guys -- or in the patients having more severe at baseline.

DR. UNGER: The graph I'm looking for, the Y-axis would be percent of patients, just as it is on CP-4 on the left.

DR. OLSEN: I do not have that presentation of the data.

DR. PICKAR: Might you share your thoughts -- Doctor, might you share your thoughts, what you're getting at, because I wasn't quite clear myself.

DR. UNGER: The point of the left side of CP-4 was to show that some 64 percent of patients were impaired at baseline. So they've made an operational definition of impaired, and they've

dichotomized the population, you're impaired, you're not impaired, 64 percent are impaired. So using that same definition, then after treatment, what percentage of patients would you categorize as impaired, based on the same definition you used there, greater than 1 standard deviation?

DR. TEMPLE: And you know there's going to be improvement on that in all three groups, but you want to see the difference.

DR. MINI: Yes. We don't have that information at this point.

MALE VOICE: [Off mic.] Just to inform you, it's now a 5-minute break.

(Laughter.)

DR. PICKAR: I've just been informed it's a 5-minute break. If I don't get out of here, it's going to go to 2. So let's take our break, come on back. FDA presentation, then open public hearing.

(Whereupon, at 2:32 p.m., a recess was taken.)

DR. PICKAR: Ladies and gentlemen, take your seats, please. And we'll prepare to hear the FDA

presentations, and we'll begin with Dr. Farchione.

FDA Presentation - Tiffany Farchione

DR. FARCHIONE: I'm back again. For the FDA presentations, I'm going to try to lay the groundwork for our presentations by giving you some background into the regulatory history of this drug development program to give you an idea of the way that things would work under ideal circumstances. This is mostly for the folks in the room who aren't in industry and who aren't regulators. This is for the folks who don't necessarily have an idea of how things work at the FDA, which is most of the world, honestly.

It's not like a company comes in, and they've got this package that they've got all completed at the end of the day, and they just present it to us and say, hey, can we get our indication? There's a lot that goes into it before that, and there is a lot of interaction back and forth with the agency most of the time. So under ideal circumstances, a sponsor will come in and request a pre-IND meeting with us, so the

investigational new drug phase. They'll come in and request a meeting with us before they ever get started going down that path.

So we grant the meeting. We give them some feedback on their development program. They incorporate that feedback into their protocols, run a few trials. The results look promising. Then they come back to us, get an end of phase 2 meeting. We all kind of sing Kumbaya and agree on the endpoints and their statistical analysis plan for phase 3.

Then they run two trials, and they're positive, and adequate, and well controlled. And they come in and they get their drug approved. That is obviously the best of possible worlds if everything ran smoothly. It doesn't always happen exactly that way.

In this case, that process got derailed pretty quickly. To give you some idea, this was a product that was already in development just for the more global indication of treatment in major depression. So the company came in with a new IND

for this separate claim for a cognitive dysfunction, and they presented this protocol for study 14122A, the one that we've been calling FOCUS throughout the morning.

Because it was a new IND, we had 30 days to review it for safety. And at the end of that review process, we issued a "may proceed" letter, which means that there weren't any issues that concerned us for safety enough that we would say you can't do this trial, so nothing that we would hold their development at that point. But we had some additional non-hold comments to provide to them.

In that letter, we said that although we agree that cognitive symptoms are generally accepted as a component of MDD, we didn't think that they had been adequately characterized, yet. We didn't think that an adequate case had been made to view them as a distinct clinical target for drug development.

So if you'll recall, this was during the era where we were pretty firmly entrenched in the idea

that this was pseudospecific, and we gave that feedback at the time. We did at least provide some guidance in terms of what to do once this is more well characterized. And we said that if you get to that point, then we also need to know about the instruments, and those instruments need to specifically assess the relevant symptoms.

So you've got to define the symptoms that are relevant first, and then present us with an instrument that's designed to assess them. And at that time, we said that we didn't think they had made an adequate case to support the instruments they had selected.

So because of that, and because of our stance with regard to pseudospecificity, I think that's probably part of the reason why the company continued their development program, but without really asking for additional input from us.

On the one hand, I've got to give them credit because they were really blazing a new trail here and sort of flying blind without our guidance. But on the other hand, we didn't really have

guidance to give at that point.

The next interaction that we had with the company was when they submitted the protocol for study 202, which we've been calling CONNECT all afternoon, and that was submitted in April of 2012. And, again, at that time, we provided comments back to the sponsor after we had reviewed the protocol and said that we would like to reiterate that cognitive dysfunction associated with MDD is not yet recognized as a distinct clinical target for drug development. And we actually went so far as to say at that point that it's likely that your proposed investigation would not support the claim you are seeking.

So fast forward another two years, and the next interaction that we had was a guidance meeting. The stated goal of the meeting was to obtain feedback from us on the adequacy of the clinical program to support a promotional claim on cognitive dysfunction. Our comment at that time was that we really felt it would be necessary to gather adequate data to fully characterize the

entity of cognitive dysfunction in MDD and to also identify all of the relevant and clinically important cognitive domains and establish valid and reliable instruments for objectively assessing the relevant domains; so basically, the same advice again, prepackaged, reworded, but it's the same message.

We did at least acknowledge at that point that cognitive dysfunction in MDD, it's an evolving field. We knew that, and that we didn't have a specific regulatory path towards a claim that we could outline for them. And particularly with regards to the DSST, we didn't have a path forward.

So we did at least go through and describe some of the issues that we felt would need to be addressed, and those included things like the relationship between the changes measured on the formal cognitive tests and meaningful clinical change. So this is something that we keep repeating throughout the day. We questioned whether there was a need for a functional co-primary measure in order to ground this in

clinical meaningfulness.

We also talked about the types of study designs that would be acceptable for assessing the effects of antidepressants on cognition. We talked about the legitimacy of focusing on cognitive dysfunction when other residual symptoms might be problematic and whether we should be looking at the acute phase, which is pretty much what we've done here -- you started from patients who are acutely depressed -- or whether maybe you should be looking at folks who are already in remission and just have residual or leftover cognitive symptoms. And then there was a question about what was the appropriate study duration.

So all of these things we really felt like hadn't quite been resolved or justified to our satisfaction at that point. And the overall take-home message was that we were still concerned about pseudospecificity.

Now, you fast forward to the stuff I talked about this morning, and you've got a whole new context now. So a few months after this last

guidance meeting we had with them, that's when we had this ASAP meeting and the workshop on cognitive dysfunction, where we saw all of the data that was presented and said, okay, well, maybe we're moving from no to maybe. We might be willing to accept this as a potential treatment target.

Shortly thereafter, you have the MGH Academy of Psychiatry workshop, and then the Institute of Medicine workshop, all of these things. The endpoint of all of those discussions were the same, that, okay, we've been convinced. We are willing to consider applications that would be seeking this claim, but a bunch of caveats here, lots of issues that are related to study design, and endpoints that are still unresolved.

Of course, now that we've made these statements publicly and everybody has heard them, now our lovely folks here on this side of the table come back, and they said, okay. We've got this application, we've got this program, and now you've changed your mind about pseudospecificity. Can we go ahead and put in our application?

What we said at that point is that we do believe that all antidepressants are going to improve cognition to some degree, but now we acknowledge that it's possible that some drugs might have a greater effect at improving cognition than others.

So that was where we had moved past where we had been before. Then we went on to say that if you believe that your drug is better at treating cognitive dysfunction in MDD, then you need to demonstrate your drug is superior to other antidepressants. And this was one of the things that we talked about this morning, do they need to demonstrate statistical superiority over another drug or not.

At that point, that was the advice we had given. I'm not sure that that's still where our stance is, but again, it was one of these unresolved issues that we need to consider. So the take-home message, again, is that with regards to all of these unresolved issues, it's still pretty much remained unresolved in a lot of respects.

They're all going to be things that are review issues, so part of the reason why we're here today. And we did tell the companies that, yes, we're going to want to talk about this in public. We're going to want to address all of these issues in an advisory committee, and here we are.

So with that, I will hand it over to Wen-Hung, who's going to talk to us more specifically about our review of the primary endpoint, the DSST.

FDA Presentation - Wen-Hung Chen

DR. CHEN: Good afternoon. This part of the FDA presentation will focus on FDA's review on the primary endpoint used to support the labeling for [indiscernible] for cognitive dysfunction in major depressive disorder.

The clinical outcome assessment review is very focused and very specific to support a labeling claim, where the endpoint that is used is based on reliable and well defined clinical outcome assessment that can be used to describe the treatment benefit that shows how the individual feels, functions, or survived and can be clearly

described in the label to inform treatment decisions.

In the review of the endpoint and the clinical outcome assessment, the first questions we want to ask is what are we measuring. Dr. Pacheco this morning already presented what the human cognition function is. Human cognition function is complex and multidimensional and involves perception, pattern cognition, attention, learning memories, language, motion [indiscernible], executive functions, and processing speed, and also presented with her a couple of times today already, that there's no single neuropsychology test that measures pure cognitive function.

Also, there's no one single cognitive neuropsychology test that measures all cognitive functions. So the general view is that a battery of tests is probably necessary in order to assess the overall cognitive functions.

These are slides just showing the primary and secondary endpoints of the two pivotal studies. It has been shown, so I will just skip quickly.

The DSST is of course the focus of this review. There are also other endpoints that also have been presented, including all other neuropsychological assessments and also patient-reported outcome, and also a performance-based functional outcome, functional assessments, the UPSA.

The UPSA, we have been talking about in order to see if the improvement in DSST is clinically meaningful. So maybe some kind of functional assessment is necessary, so I will talk in more detail about UPSA later.

Also, I want to mention that for the work limitation questionnaire, I classified it as patient-reported outcome assessment because basically it is patient reported. That is a big difference from what we've seen earlier, that function working limitation questionnaire is actually listed as functional. It is assessing the work productivities, but it's also patient reported.

Again, we heard a lot about DSST already.

It is a neuropsychological test. Then we classified this as a broader category of a performance assessment PF, that the patient performing the tasks gets score. And then we see the change in the performance. I won't go through the detail. Then we see the assessment. We see the DSST. And this one has been actually used. It's from the Wechsler Intelligence Scale, or WISC-3.

So the first question about whether it is a reliable, well defined clinical outcome assessment -- the first question we have to ask is what does it really measure in patients with MDD. Again, we heard a couple of times there's no definite answer to what the DSST actually measures in patients with MDD. Dr. Jaeger just earlier mentioned that it's not specific.

In the literature, processing speed has been mentioned consistently than most. And also the copy speed, visual motor coordination, motivation effort, we heard about the -- and also age is one of the most -- a very significant factor that

affects the performance, especially an age older than 60.

Also, DSST has been shown to associate with other neuropsychology tests also assessing attention, working memory, and executive functions. And most of the neuropsychology tests are intercorrelated overlapping, so I'm just repeating what we heard. And it's actually what we have been seeing and the general views.

In fact, the exploratory analysis on the WISC-3, the Wechsler Intelligence Scale, exploratory analysis shows DSST loaded [indiscernible] only on processing speed. That's not loaded on the working memory or the verbal comprehension, or perception organization. Dr. Jaeger already showed actually DSST is highly correlated with working memory and learning for schizophrenia patients.

So this actually highlights that we cannot pinpoint what DSST actually measures because there are different versions of DSST out there, and then there are different patient populations that have

been used and described. We see in some studies it is not correlated with working memory and attention, and in some studies, it does. So it's difficult to definitely say what it measures.

Also, different patient population has different types of cognitive dysfunction or different levels of cognitive dysfunction. And different forms of DSST have different levels of difficulties, and we don't know whether the different levels of difficulty require more or a different type of cognitive functions. Again, there's not much data on what DSST measures for MDD, but probably we can reasonably say that the processing speed should be at least one of those.

The second question in our review of whether it is a reliable and well defined assessment is that we also need to answer the question of how much change is required for clinically meaningful improvement in patients with MDD. To this day, there's no empirically-based threshold or changes in DSST that represents a meaningful improvement. For example, improvement of 4 numbers correct,

improvement of 6 numbers correct. It's not clinically meaningful.

Different from the placebo group, although it's statistically significant -- I mean, not just for this submission but for all other drug reviews, we always ask the question of whether the significant p-value different from the placebo group is sufficient. We also need to see whether the changes, the difference, is also clinically meaningful.

We are not able to find any empirically-based thresholds for DSST number correct to ask whether the change is clinically meaningful in MDD patients.

Essential to the question of clinically meaningful is whether the score changes that we observe in DSST after 8 weeks of treatment is that it can be directly translated to the improvement in the real-world functions. That actually takes us back to the UPSA. And UPSA was used in the study 202, CONNECT, one of the additional endpoints.

UPSA is actually a performance-based assessment designed to assess function capacity for patients with severe psychiatric disorder, mostly for schizophrenia or schizo-effect disorder patients. Here is an example of that. So UPSA involves role-play tasks that are administered as simulations for events that the person may encounter in the community.

This slide shows the role-play tasks for communications skills where the subject is asked to do various tasks involving using a telephone, and there are other tasks, involving counting the money or calculating change.

The one thing I would make a note is that for the CONNECT study, two versions of the UPSA actually were used. The UPSA brief version, which only has two domains, was used in Europe, and the longer version of UPSA, UPSA VIM, was used in the United States, which has five domains.

On one side, you have two versions and two domains, on the other side, you have five domains. The total score was calculated with two domains and

five domains, and then combined as a total score subject to these particular tasks.

So it makes it a little bit difficult to interpret the results because you have longer versions combined with shorter versions together, and then do [indiscernible] test. So it's kind of difficult to say whether this improvement is really related to real-world functioning. And also, similar like DSST, there's no established threshold for how much improvement in UPSA is actually clinically meaningful.

In summary, there's no definitive answer to what DSST actually measures in patients with MDD, and there's no empirically-based threshold for the change in DSST score that represents meaningful improvement in overall cognitive function or meaningful changes in everyday functioning for patients with MDD. Thank you.

DR. PICKAR: The next FDA speaker is Dr. Gaymon-Doomes.

FDA Presentation - Aeva Gaymon-Doomes

DR. GAYMON-DOOMES: Hi. Good afternoon.

I'm Aeva Gaymon-Doomes, and I'll be here talking about the clinical safety and efficacy, as soon as my slides come up.

Over the course of the morning and earlier this afternoon, we heard informed presentations on cognitive dysfunction in major depressive disorder and its symptoms. So hopefully, we've all come to understand that cognitive symptoms occur in about two-thirds of those diagnosed with major depression, and they may persist even after treatment and even while the core mood symptoms are in remission.

There's no formal way to diagnose or measure this cognitive dysfunction in major depression, which poses a predicament for clinicians. And we're here today to really discuss that, cognitive dysfunction in major depression as being an unmet need and the current application under review.

Vortioxetine was approved here at the FDA in 2013 for the treatment of major depressive disorder. The recommended doses of 20 milligrams a day can be lower, depending on the patient's

tolerability or metabolism. The efficacy was established in six short-term trials and one maintenance study.

The mechanism is thought to be related to inhibition of 5-HT reuptake in the CNS. And while the applicant hypothesizes that action at the 5-HT3 receptors are involved in vortioxetine's cognitive effects, this is unproven and not included in the label. And the mechanism of action, as we know it, relies on nonclinical data and binding studies, which are not easily translated into clinical models.

The safety of vortioxetine has been well established. It is an approved drug. There were no new safety signals identified over the course of this review, and the most common adverse reactions in the premarketing clinical trials were seen again in this application: nausea, constipation, and vomiting. The labeled warning and precautions of drugs in this class are serotonin syndrome, abnormal bleeding, activation of mania/hypomania, angle closure glaucoma, hyponatremia, and there's a

black boxed warning for increased suicidal ideation and behavior in children, adolescents, and young adults.

The study that initiated this was actually submitted in the original NDA for major depression. It was the, as we've heard today, ELDERLY study and referred to as the 12541A. It was a randomized, double-blind, parallel group, placebo-controlled, duloxetine-referenced, fixed-dose study. And this study evaluated acute treatment of major depression in elderly patients. And the relevance today is, included in this was the Digit Symbol Substitution test as one of many secondary endpoints.

After 8 weeks, there was a change from baseline in the DSST greater in patients taking vortioxetine 5 milligrams as compared to placebo. In the duloxetine arm, it was also numerically better than placebo, but the effect was numerically smaller than the effect of vortioxetine. This then encouraged the applicant to pursue a new claim.

The first of the two pivotal studies submitted for the claim of cognitive dysfunction in

major depression was the FOCUS study 14122A. It was an 8-week randomized, double-blind, parallel group, placebo-controlled, fixed-dose study. It was the first of the two specifically designed to assess the effect of vortioxetine on cognitive dysfunction in adult patients with major depressive disorder.

It included 602 patients that were broken down into treatment arms of placebo, vortioxetine 10 and 20 milligrams a day, and included patients that had a MADRS over or equal to 26 and a current depressive episode greater than or equal to 3 months.

This is a study design schematic for the FOCUS study that does illustrate three treatment groups and the fact that the vortioxetine arm had a 1-week lead in if you were going up to 20 milligrams before ending treatment at 8 weeks.

The primary endpoint of the FOCUS study, we're talking a lot about that in our presentation. It was a change from baseline to week 8 in a composite cognitive measure that was based on the

DSST and RAVLT. This composite score was weighted. Half of it was the DSST, and the remaining half was given in one-fourth and one-fourth the RAVLT learning and memory.

From the stats review of this composite Z-score, again, the FDA remained concerned about the clinical relevance of this composite Z-score as the primary endpoint using the DSST and about the calculation for the composite score, and whether or not the independent assumption required for statistical analysis was met.

The prespecified secondary endpoints that we've been discussing today, most importantly the DSST, for this study showed differences from placebo at week 8, 4.20, in favor of vortioxetine, 10 milligrams a day, and 4.26 in favor of vortioxetine 20. For the RAVLT, the learning scores were not significantly different from placebo for either of the group. And then, thus, based on their prespecified protocol, the testing hierarchy stopped.

This slide shows the additional secondary

endpoints that were used in both studies, except for the one-back task, which was used in study 202 that we'll be discussing next. This slide does illustrate the cognitive domains that do overlap somewhat with the DSST in terms of attention, speed, processing, and executive functioning.

For the neuropsychological test, in this study, you can see the difference from placebo at week 8 in the two treatment groups. This table shows statistical analysis, and endpoints were considered exploratory and were not incorporated into controlling for the overall type 1 error rate. Nevertheless, they do seem to suggest the superiority of vortioxetine in many of the measures.

The LS mean results I should point out for the Trailmaking Test A and B, those are in seconds as well as the Stroop, congruent and incongruent. And the SRT and CRT, those are in milliseconds, as a point of reference.

The additional secondary endpoints included were subjective and based on self-report. This

slides summarizes, again, that the results seem to suggest the superiority of vortioxetine at a nominal significance level of 0.05.

Study 202, which has been called CONNECT all day, and we can use those terms interchangeably, this was a second pivotal study that was included in this application. It was also a multicenter randomized double-blind placebo and now active-controlled, parallel group, flexible dose study. So this study included duloxetine as a reference at 60 milligrams a day, and then 2 treatment arms of vortioxetine, 10 and 20.

Again, this study had 602 patients, about the same number as the previous study. And this study design schematic illustrates this randomized double-blind placebo and active-controlled parallel group flexible dose study CONNECT, with the primary objective of assessing the effect of vortioxetine versus placebo on cognitive dysfunction in a population of patients with self-reported cognitive dysfunction. And as you can see from this slide, there was also a 1-week lead in for vortioxetine

10 milligrams in both of the vortioxetine treatment groups before going up to 20 milligrams.

The primary endpoint in CONNECT was not a Z-score. This study used the primary endpoint as just the DSST, the number of correct, from baseline to week 8. The LS mean difference versus placebo was 1.75 in favor of vortioxetine. And the LS mean difference between the duloxetine and placebo groups was 1.21.

The prespecified secondary endpoints, there were two, PDQ and CGI-I, respectively. And the results were both of those endpoints were statistically significant. And of note, the testing hierarchy applied only to the vortioxetine group.

The other secondary endpoints in CONNECT included, as we discussed before, the cognitive tasks from the other study in addition to the one-back task. In the vortioxetine versus placebo group in this study, only the Trailmaking Test B was better than placebo, and no comparisons reached nominal significance for duloxetine versus placebo.

On this slide, this illustrates that the other secondary endpoints of self-report in CONNECT did show that even though vortioxetine was numerically better on DSST, the duloxetine was similar or numerically better than vortioxetine versus placebo.

Again, this study did explore the question, can subjective assessments of cognitive dysfunction be used to reliably monitor improvement in cognitive function in patients with major depressive disorder, and on both the PDQ total scores, both duloxetine and vortioxetine were better than placebo.

This slide discusses the other secondary endpoints on CONNECT. The UPSA is a the five domain skills assessment asking about household chores, communication, finance, transportation, planning, recreational activities. Each domain's scales range from zero to 20 points across with a total of points of zero to 100. On the review of this, it was not clear what a 3-point difference on a 100-point scale meant clinically.

Of note, on the working limitation questionnaire, there was only one subscale that moved in the CONNECT study. Also of note, only the vortioxetine was significantly different from placebo in reducing the difficulty of time management. And neither vortioxetine nor duloxetine separated from placebo in the remaining four scales.

This slide looks at the DSST results from both of the studies and is a summary of them. It shows that the baseline scores were quite similar between 41 and 43 across the treatment groups. Although the DSST results were statistically significant in both studies, the magnitudes of the observed treatment effects were larger in the FOCUS study but not in the CONNECT study, where the difference from placebo in the vortioxetine arm was 1.75.

In summary, there were three positive results for vortioxetine; initially, the ELDERLY trial that was first submitted in the original NDA in exploratory, and in the two pivotal trials that

were submitted in this application, CONNECT and FOCUS, were both positive.

There was a greater magnitude of DSST change observed in the FOCUS trial as compared to the CONNECT trial. The observed improvement on DSST at week 8 was better in the vortioxetine group than the duloxetine group in CONNECT. And CONNECT also did include functional measures. Although they were not prespecified, the results do seem to suggest superiority of vortioxetine versus placebo. That will conclude my presentation.

Clarifying Questions

DR. PICKAR: Thank you very much. We're open now to clarification questions, so please raise your hand. Let's talk to the FDA folks and get some clarification on the presentations. The floor is open. Dr. Dickinson?

DR. DICKINSON: So I'm having trouble conceptualizing this in the absence of something specific that we are supposed to be judging as to what the label might actually say. I know that is a subject that would need to be negotiated with the

company if it went that way, but it's a little bit -- so there are a variety of issues that have been touched on. Among other things, there were some limitations in these studies in terms of who was allowed into the studies.

Would those be things that were attached to this labeling? There's a question about whether there was cognitive impairment at the beginning of the trial? And even getting past those kind of entry issues, what would one say about some improvement on the DSST? What would be the language that we would be asked to consider as an addition to the label?

DR. FARCHIONE: I think that with regards to that, again, like you said, a lot of this is going to depend on negotiations with the company if we choose to take an approval action on this application. But in terms of general principles when we approach labeling, we want to be able to describe the population that was included in this study so that that way, you can have some idea of whether or not -- if you're a clinician reading the

label, you can have some idea of whether or not your patient that's sitting in front of you is similar enough to the people who were in that study that you might expect to see a similar level of effect.

We would also include a brief description of the endpoint that was used. So in this case, we would have to probably come up with some one or two-sentence pithy explanation of this is the DSST, and it measures X, Y, and Z, or just X, whatever we decide in regards to that. If it does just land in that clinical study's section, then the only thing it's going to do is say here are the patients that were included in the trial.

This is what the endpoint was. This is what the outcome was, and not really offer an interpretation of that. That's up to the person reading it to make that judgment.

DR. PICKAR: It's a little tricky. The last slide, Dr. Chen's presentation, there's no definitive answer to what DSST actually measures in patients with MDD, and there's no empirically-based

threshold for the change that has meaningful in functionality. That last slide is a pretty meaningful slide. Could somebody -- anybody comment on that? It's hard to move ahead when you see something like that.

DR. FARCHIONE: Well --

DR. PICKAR: That's slide number 12 from Dr. Chen's presentation.

DR. FARCHIONE: Yes. I think that part of the reason, in terms of what DSST actually measures in patients with MDD, is that it hasn't been standardized in that population. So if we're going -- we have some idea of what it might measure generally in people without depression, but can we generalize that to this population? We just don't have a definitive answer, but we have some general ideas.

DR. PICKAR: Well, let me ask the neuropsychologists. It would seem to me that you can. If it has a pretty specific -- it is what it is, and it may be global and overly sensitive and less specific. So we would assume that there's

cognitive dysfunction related to that measure in MDD.

Is that a correct statement or am I just -- I'd like to get something more definitive, more positive than that statement.

DR. HINKIN: Yes. I mean, it's definitely measuring cognition in patients with MDD as it would in others. There may be some slight factor loading changes compared to normals or another population. But for the most part, I think it's reasonable to conclude that it is measuring the same basic cognitive constructs in depression, depressed folks versus non-depressed.

DR. PICKAR: Dr. Grieger?

DR. GRIEGER: It seems to almost draw too much attention to it. I'm a little confused because we put all kinds of side effects in, and we just say, here's your list of things that could happen. And why we would draw attention to the specifics of a particular -- I kind of like what the industry put up, which was it has shown to work on this test, period, and this test probably

measures these things.

I wouldn't go any further than that. I was kind of looking for that in their package. I didn't see that, but I think the first slide they put up today was very straightforward. It says exactly what it does, like 2,000 patients took this drug, and their HAMD scores improved by 10 points, whatever.

DR. PICKAR: Dr. Conley?

DR. CONLEY: So yes. I'd like to go back. I also was wondering about the statistical measures or the presentation, and it was slide 12 in that. It seemed to be much more a judgment base about there isn't a threshold. My worry about that, that is from an industry standpoint, is that it's like almost the first mover syndrome. It goes back to what we said before. We don't know what works in this area, so of course there isn't an empirically validated scale. There couldn't be until something actually works. So it just seems like a tautology.

So that's a real concern that I have here. And I would expect in the statistical section, you

mentioned that you thought the secondary measure seemed to go along with the primary measure, the analysis working okay. That all makes sense. It's not like it was all bad. But there isn't an empirically-based threshold. I guess I'm just wondering what on earth; of course, there isn't.

DR. TEMPLE: Empirically-based threshold for what's a meaningful change, you mean?

DR. CONLEY: Well, for what meaningful change is in this specific condition of depression I guess is what the analysis --

DR. TEMPLE: Yes. I don't want to be too repetitious, but it's not easy to say what that is.

DR. CONLEY: Right.

DR. TEMPLE: Also, it seems worth reminding everybody that the mean is not the full explanation of what's going on, and it's very hard to know if you have a range of responses that go from 2 to 10. How do you decide?

DR. CONLEY: So what would have helped on that --

DR. TEMPLE: Dr. Papadopoulos is here.

She's worries about that all the time. But it's really murderously difficult to do, and I don't think we do it very often in a way that anybody would say definitive. You can ask patients. That's one of the things that are done now. You incorporate that kind of question into a PRO, say, do you really feel better, all of those. That's got a distribution, too.

DR. CONLEY: I think you're right. And I think, actually, you asked the sponsor a couple of questions that I thought were very good ones, like a responder analysis. And they had I think two out of three answers or something like that.

So there were some other ways of probing it. But again, I'm talking about the field in some ways more than this particular drug. But I'm just worried as you're trying to be innovative that you've got to be careful about not saying there isn't this evidence-based standard before there's evidence.

DR. FARCHIONE: Well, I agree in a lot of ways. And I think that the whole point is that, if

we want to point out the kinds of limitations that we're dealing with in terms of defining a new claim, there are a lot of -- if we want to put something new in a label that's never been in there before, I think the bar necessarily has to be fairly high but it shouldn't be insurmountable.

The idea that there might not be an empirical threshold yet doesn't mean that we can't look at it and say, well, maybe we can match this up and try to figure out what degree of change on the DSST correlates with what degree of change on the CGI, or somehow anchor it in some way. It's not an insurmountable issue to deal with. It's just something we have on our plate.

DR. CONLEY: Yes. Just a last comment to come back. What you're saying makes sense. I mean, to me, that's better than saying there is no threshold, therefore we can't make it. And you were asking questions about that. That's more reasonable.

DR. FARCHIONE: It's not insurmountable.

DR. PICKAR: Dr. Stein?

DR. STEIN: Just a question for Dr. Gaymon-Doomes. I just wanted to clarify or ask you to clarify something in your last slide. Could you put up your last slide from your presentation?

MS. BHATT: What's the slide number?

DR. STEIN: It's 22. So the third point, observed improvement on the DSST was better in the vortioxetine group than the duloxetine group in CONNECT. Significantly better, numerically better? Just go back to slide 21 because they don't look different to me.

DR. GAYMON-DOOMES: Numerically.

DR. STEIN: Right. So one has got a change from baseline of 4.6 and the other's 4.06. And I don't see a statistical test there.

DR. TEMPLE: That's an important question. You cannot conclude from this that it's better. You know that one won and the other didn't.

DR. STEIN: Okay.

DR. TEMPLE: That's not the same thing.

DR. STEIN: The third point on the last slide is not correct the way it's written?

DR. GAYMON-DOOMES: It is, but it's numerically.

DR. STEIN: Okay. Thanks.

DR. PICKAR: Dr. Hinkin, did you have -- no.

Other questions? Any comments from the FDA, the team?

(No response.)

DR. PICKAR: Thank you very much for the presentation.

Open Public Hearing

DR. PICKAR: We're now moving to the open public hearing portion of today's meeting. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the 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 relationships that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have 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 today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and

respect. Therefore, please speak only when recognized by the chairperson, and I thank you for your cooperation.

We shall begin with speaker number 1.

DR. MATTINGLY: Good afternoon. I'm Greg Mattingly. I'm a psychiatrist. I come to you from St. Louis, Missouri. In St. Louis, I teach the pharmacology classes for the medical students at Washington University. I'm the course master. I've been in clinical practice for 23 years. I spend one-third of my time doing clinical trials, where I've done over 200 clinical trials as a principal investigator.

I have conflicts of interest with pretty much every pharmaceutical company within this room. I've been a principal investigator for Lundbeck and for Takeda. I was part of the phase 2 trials for Brintellix and serve on advisory boards for most of the pharmaceutical companies.

Most importantly, I spend two-thirds of my time every day in a very busy clinical practice. I've been taking care of patients for the last two

decades struggling with major depression who have residual symptoms that don't improve with our current treatments. Every one in this room has taken care of patients with major depression who have cognitive symptoms that have not improved with our current treatment options.

Dr. Ionescu's questions about what have you tried with your patients, I'm going to present three patients very quickly in my limited amount of time. One is a young man named Joshua. Joshua provided written testimony for your group today. He was going to be here with us, but he's taking his college tests in his senior year today.

Joshua came to see me at age 16 after having two major episodes of depression, had a tested IQ of 160, but was failing his high school classes because he was struggling with bad depression. In between episodes of depression, Joshua still had cognitive symptoms. I tried him on every cognitive enhancer you could think of: low-dose psychostimulants, Modafinil, augmentation with thyroid, augmentation with atypicals.

Joshua finally got fed up with taking antidepressants and about two years ago came back to see me as he had just failed junior college. At that point, I talked Joshua into trying vortioxetine. Two years later, Joshua is now on the dean's list. He's going to graduate from college, and he just had a full-time employment opportunity working as a CAD CAM programmer over this next summer. Joshua, you will see in his written testimony to you, will say the single most important episode of vortioxetine, it has improved his cognitive symptoms in a way that nothing else has.

My second patient is a young man named Mike. Mike came to see me a little over a month ago. He was taking vilazodone. Mood symptoms were better, anxiety symptoms were better, but he couldn't focus. Cognition was bad. He had no premorbid history of ADHD, no premorbid history of cognitive issues before depression began taking ahold of his life. I changed him to vortioxetine 10 milligrams a month ago, and he's now doing dramatically better

with regards to cognition.

My last patient is 62-year-old physician, recurrent mood disorders that I've taken care of for the past 10 years. She was thinking about going on part-time disability because of cognitive challenges associated with her depression. Since being on vortioxetine at 20 milligrams, she continues to work. She continues to work in a very active pediatric practice and is very happy with her life.

Thank you for this testimony.

DR. PICKAR: Thank you very much. Speaker number 2.

MR. BARTHOLOMEW: Good afternoon. My name is Ray Bartholomew, and I'm here to share my experience using Brintellix for treatment of MDD. I'd like to thank Takeda Lundbeck for providing transportation, meals, and lodging, which made it possible for me to be here today.

I'm 67 years old, live in Gansevoort, New York. Ten years ago, I retired from my career as a manufacturing team leader at General Electric for

39 years. Since then, I've been active in various volunteer administrative positions in my community.

Through most of my adult life, I've battled with major depressive disorder and have been prescribed various medications for treatment. For the past two years, I've been taking 20 milligrams of Brintellix once daily.

Prior to that, I'd been prescribed Cymbalta, which worked rather well for many years. However, over a period of time, I started experiencing troubles expressing myself verbally. I just couldn't find the right words. I often felt confused and struggled with organizing daily activities, handling our finances, and reading comprehension, having to reread things several times in order to understand. I also was experiencing extreme brain fog.

My wife bought me a white board to help me with planning and remembering steps for day-to-day appointments and activities. However, as time went on, these symptoms worsened to the point where I was no longer able to serve in the various ministry

and volunteer activities I had been involved with since my retirement. I was feeling frustrated and overwhelmed. I was basically homebound for around a year, relying on my wife to help me in making decisions.

My wife was very concerned that I might have had a stroke, so we went to a neurologist, who had testing done to rule out things such as Parkinson's or Alzheimer's. The test results revealed that I had some serious cognitive impairment. It was frightening time for both of us.

After ruling out all those causes, my primary care physician advised me that Brintellix may help relieve some of the symptoms that I was experiencing. I made the switch from Cymbalta to Brintellix. After around six weeks, I started to notice a marked increase in my ability to mentally process information. The brain fog was clearing. My ability to process information improved dramatically, and I was able to make good, sound financial decisions again.

Day-to-day decisions were no longer an

issue. Reading comprehension improved, and I returned to the voluntary activities that I was so passionate about. Currently, I'm serving as a leader in the recovery program that I helped establish called The Landing. We help youths in the community that are having difficulty with family, and peer-to-peer relationships and with school, and with sound decision-making, and I'm feeling thankful for being part of that team.

Brintellix has made a great difference in the quality of my life, and I'm here today hoping that others may experience the same results. Thank you for the opportunity for letting me share my story with you.

DR. PICKAR: Thank you very much sharing it. We appreciate it. Speaker number 3 was not able to be here, so we're moving to speaker number 4.

MR. BARTLEY: Good afternoon. My name is David Bartley, and I'm here today to talk about my experience with Brintellix. The sponsor has covered my travel and hotel, but no financial interest in the company is had by me.

On August 31, 2011, I was admitted as a patient in a psychiatric hospital, and I was there because I had answered yes to two questions posed to me by the psychiatrist in the emergency room: Did I intend to harm myself, and did I have a plan? When people found out I was in the hospital, they were shocked because at the time, I was running a nationally recognized end-of-life animal sanctuary.

On June 2, 2010, the sanctuary was featured as the cover story in the life section of USA Today, but I was a good actor, and I hid my illness from just about everybody. But the plan was an effort to relieve me of the pain and long suffering of MDD. When I got out of the hospital, where I stayed for 14 days, I realized that I had to focus on my own care, so the animals were placed in other facilities and the sanctuary closed.

That commitment to self-care has continued to this day. My life is all about taking care of myself, adequate rest, proper nutrition, exercise, seeing my therapist, involvement in a depression support group, and for me the right medication,

which is 20 milligrams of Brintellix. My health, my life now is about serving other people and going out into the community to reduce stigma and encourage those to get help that they need.

In regards to medication, when I was in the hospital, I continued Zoloft that I had had for 20 years, and my medication was increased to 200 milligrams. But soon after, I had continued down a recurrent path of major depression, and I went in to see my primary are doctor, who switched me to Brintellix, and the relief was almost immediate.

But in addition to the mood lift that I had hoped for, I got what I called cognitive juice, a bump in my ability to process information, and it was extraordinary. Previous to Brintellix, my thought process could be described as delayed, a sort of mental hesitation, very much like the built-in delay in a radio talk show. It was almost as if there was a governor that regulated the speed of my thoughts. But now that governor has been lifted, and my mind operates. It hums in a very positive way.

To give you a more tangible example, I'd like to give you a real-life example. When the sanctuary closed, I went back to work as a loan officer, and the world of real estate and finance, as many of you know, is complex and confusing. The reliance on memory, problem-solving, and processing is extraordinary. And added to that is the need to have a working knowledge of a vast number of regulations and guidelines.

When I went back to work, I was classified as an adequate loan officer, but I've been able to move along the continuum to be an exemplary loan officer, so much so that in April, I'll be enjoying an all-expense paid trip to Hawaii, courtesy of the mortgage company that I work for. That experience has allowed my mind to match my experience, and I have a chance to view myself differently, capable and worthy. And that is an extraordinary experience. Thank you so much.

DR. PICKAR: Thank you so much. Speaker number 5.

MR. DOEDERLEIN: Thank you, and good

afternoon. I am Allen Doederlein, president of the Depression and Bipolar Support Alliance, or DBSA. DBSA does receive grant support from Takeda, however, my presence here today was covered by DBSA unrelated to that grant support.

We at DBSA hold that the end goal of treatment should be total wellness. Of course, this idea is empowering and hopeful, but there are also real and significant clinical imperatives to hold this goal as the endpoint of treatment. Residual symptoms can lead to higher rates of relapse in major depressive disorder, longer and more severe courses of illness, more co-occurring conditions, and a higher risk of suicide.

So any unmet needs in terms of residual symptoms or symptoms of major depressive disorder are of great concern. But cognitive dysfunction is especially concerning, to the extent that it is not specifically addressed by many clinicians or understood as an aspect of depression by most people who live with it. Moreover, cognitive impairment can stand in the way of activities that

are important to many people's definitions of wellness, including communication and meaningful work.

I'm here today not only on behalf of DBSA, but to represent my own personal lived experience of major depressive disorder and the cognitive impairment associated with it. In college when I was first diagnosed with depression, I, who had always felt smart and done well in school, suddenly felt incapable of the kind of study and achievement I'd been used to.

In my first professional job when I experienced depression, I feared being caught as a fraud who couldn't actually fulfill on the duties he was assigned. I worked twice as long and achieved half as much because I felt like I was constantly in a fog, and the distance between thought and action was an ever-widening chasm.

Time and time again, I'd find that my focus, memory, decisiveness, ability to order tasks, follow through, problem solving, ability to follow conversations, and my activation all suffered

impairing my work, my relationships, and my self-esteem. These impairments fed the hopelessness and feelings of guilt and worthlessness that were part of my depression, so I often felt like I was trapped and sinking in quicksand. Once I learned that cognitive impairment is associated with major depressive disorder, my abilities to recognize depression earlier and work with my doctor on better treatment both improved.

Stories of such cognitive impairment are not unique to me. We hear from hundreds of DBSA members who report similar experiences of cognitive dysfunction, and it is real and debilitating. We at DBSA offer that to recognize cognitive dysfunction in major depressive disorder as a distinct suite of issues with real unmet need in clinical focus and understanding will open the door to needed patient education, better treatment, and better thriving lives for people like me who experience major depressive disorder. Thank you.

DR. PICKAR: Thank you very much. Speaker number 6.

DR. NORTH: Hello. My name is Dr. James North, and I'm a board certified family practice physician. I practice full-time in an outpatient and hospital setting in upstate New York as a member of a large group practice. I also work very part-time as a paid consultant and advisor for several pharmaceutical companies, including Takeda Lundbeck. Takeda Lundbeck is covering my expenses for being here today, but I'm not being compensated for my time.

It's an honor to have this opportunity to speak to you today because I am passionate about this label change for Brintellix. It's an addition that has made such a big difference, such a life-changing difference for my patients. I have several dozen patients who've had really transformative experiences with Brintellix, including Ray, who spoke to us just a few moments ago.

Now, throughout the day, you've seen lots of data surrounding cognition in depression. However, studies look at patients in aggregate, and I as a

clinician treat patients as individuals. I'm charged with treating those patients, and this residual cognition issue is out there, it's real, and I see it over and over again in a clinically relevant way. And I've seen Brintellix make a difference with these patients.

When I think about cognition in depression out there, I don't do a Digit Symbol Substitution test. My 50-year-old diabetic was struggling with four fluctuating blood sugar readings throughout a day, three mealtime insulin dose coverages, and another bedtime dose of insulin. So she was looking at all kinds of numbers. Throughout the day, she was not controlling her diabetes well. When I switched her antidepressant to Brintellix, her diabetic control improved.

When I think about depression and cognition out there, I don't need to do a Trailmaking B Test. I'm already asking patients to make important decisions about their health care. I had a depressed 72-year-old widow who was struggling with severe osteoarthritis and was slowly losing her

independence. She was becoming wheelchair bound because she was paralyzed with indecision about whether or not to undergo surgery. When I switched her antidepressant to Brintellix, she now had the means to say, yes, I'm willing to have that surgery despite my age.

Then there's Ray who spoke to us so eloquently a few minutes ago. Before Brintellix, without Brintellix, Ray would not have been able to make this trip, let alone give you the presentation that he did. Despite an adequate trial of several antidepressants, Ray was cognitively impaired. He had withdrawn from his family, from his social life, from his church, and from his life in general.

Brintellix gave Ray his life back. As Dr. Fava suggested, if I hadn't known that Brintellix had the potential ability to make a difference for Ray, I might not have had the opportunity to have him try it, and that would have been a tragedy.

When you vote this afternoon about this

label addition, I want you to think about Ray. Cognition in depression is more than just a metric. It's more than just a number. It's a suffering person with a life they want to get back. Thank you for listening to me about my real-world experiences with Brintellix. And thank you especially, Ray, for trusting me and finding me. Thank you.

DR. PICKAR: Thank you so very much. Speaker number 7.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings. I was previously a neuroscientist at the Children's National Medical Center, and I'm now a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical data to provide objective health information to patients, providers, and policymakers. We do not accept funding from the drug or medical device industry, and I have no conflicts of interest.

We want effective treatments to reach

patients as quickly as possible. The cognitive dysfunction symptoms of MDD greatly contribute to the difficulties patients face, and most of the treatments show little improvement on cognitive tests. Patients want treatment for these symptoms, but need to know that the drug marketed to do so is actually effective.

The data today suggests that vortioxetine may ameliorate some cognitive symptoms, however, more evidence is required. In the FOCUS study, the main test that it demonstrated improvement was the DSST, which is under debate to determine if it provides a meaningful measure of diverse domains of cognitive function. If this test is not a comprehensive measure of cognitive function, then we can rely on the data from the CONNECT study.

The improved scores on the tests in this study are encouraging, but they need to be replicated. Thus, this would not provide enough data to fill the statutory requirements to state that the drug is effective. More research is necessary. The cognitive deficits experienced by

patients need to be fully described. The cognitive tasks improved by this drug must be clarified, and the extent to which treatment influences daily function must be determined. To this last point, a treatment can statistically improve a test score without producing a meaningful improvement in daily life.

There are also concerns about the lack of diversity of participants included in the pivotal studies. There's inadequate racial diversity. Although both studies were conducted in multiple countries, more than 85 percent of the participants were white. Thus, there are not enough patients to conduct meaningful subgroup analysis to determine the impact of the drug on people of color.

The age participants is also a concern. Cognitive dysfunction is common in elderly and BD patients. The sponsors even state that their investigation followed up on the results of a clinical trial in elderly patients. However, the age cutoff for both pivotal studies was 65 years. Furthermore, subgroup analysis by age only showed

improvement in DSST scores and in only one of the two studies. No subgroup analysis were conducted for any of the other cognitive tests.

Lastly, the time frame for both of these studies was 8 weeks. Cognitive dysfunction can continue to be a problem after a depressive episode is resolved, and depressive episodes last much longer than 8 weeks. It is important to know whether any improvements would be maintained over a longer term of at least a few months.

In conclusion, based on the data presented and discussed today, I urge you to conclude that there's insufficient data to claim that vortioxetine is effective in providing a meaningful improvement in cognitive dysfunction associated with MDD. Thank you for the opportunity to speak today and for consideration of our views.

DR. PICKAR: Thank you very much. Speaker number 8, please.

MR. DOLAN-DEL VECCHIO: Good afternoon. My name is Ken Dolan-Del Vecchio. I'm a vice president in the health and wellness organization

at Prudential, and specifically, I'm responsible for all of the behavioral health programs and services for our 20,000 domestic employees. Part of my responsibility that I want to talk about today is the leading of our team of counselors who work with employees, many of whom, as you would guess, struggle with clinical depression. And I'm hopeful in this conversation today because we're addressing this issue of cognitive.

I am not in any way being paid by Takeda. They have paid for my transportation and my lodging, and that's it. I don't stand to gain from their stock price.

When I think about this issue, I think about how there's a complex mix of problems that come with clinical depression. There's the mood problems. There's the resiliency life activity problems of sleeping and eating. And then there's the cognitive problems.

The cognitive problems are the ones that define, so many times, the threshold that determine whether an individual, a working person who lives

with depression, is going to be able to keep working.

For example, at our company, we may have a customer service representative who absolutely when they're doing well knows all that they need to know in order to answer the questions of the people who call them. But when they're having the cognitive difficulties that define this part of a depression problem, they might not even remember the call. They might not remember what the person's asking. And then they're struggling to find the information.

If a claims manager is working through a claim, they might not be able to hold their train of thought, the train of the narrative that they're reading. And if a communications professional in our organization is trying to exercise their usual creativity and pull together the language that's going to be engaging in the piece that they're writing, all of that may have deserted them.

So when these essential functions are no longer functioning, this person is moving towards

disability. And we know that disability -- in fact, I saw a World Health Organization report stating that depression is the primary cause of disability worldwide. And when a person faces disability, they lose so much more. There's a downward spiral in their functioning.

So I'm hopeful that a medication like this might contribute to an upward spiral, might contribute to the possibility of the person holding on to those functions that are going to allow them to do what they need to do to feel better. Thank you.

DR. PICKAR: Thank you very much.

The open public hearing portion of this meeting has now concluded. I thank each of you for speaking with us. It's very important. We will no longer take comments from the audience. 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.

Dr. Farchione will now provide us with a

charge to the committee.

Charge to the Committee - Tiffany Farchione

DR. FARCHIONE: In terms of just addressing what the committee is going to be doing this afternoon, this is a preview of the questions that we're going to be discussing and the one voting question that we have on our agenda.

The point of all of this, we have all of this discussion in advance to really talk about all of those unresolved review issues that I mentioned in my talk and that we discussed throughout the afternoon here in terms of how the applicant attempted to address them.

At the end of the day, the final question is just going to be to take a vote on whether or not you guys feel that substantial evidence has been presented by the applicant to support the claim of effectiveness for vortioxetine in the treatment of cognitive dysfunction.

So we'll run through each of those discussion points one by one and finish with the voting question.

Questions to the Committee and Discussion

DR. PICKAR: Thank you very much.

We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is indeed open for public observation, public attendees may not participate except at specific request of the panel.

There's one item here where we will be voting, and 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 are unsure of your vote or if you wish to change your vote, you may press the corresponding button until the vote is closed.

After everybody has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. You'll see it in process if you haven't done it before. The vote from the screen will be read by Ms. Bhatt, and after the

vote is read, 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 to all questions that have been answered. In this case, there's only one voting issue.

Question number 1 is up there, and I think we're actually right on target, so let's go with it. Discuss whether the DSST is an adequate measure of cognitive function in MDD. Table open. After all this, what do people think?

DR. CONLEY: Well, I just kind of have a clarifying question to the question as it were. I thought that what the sponsor presented in this -- and again, more as a general thing -- was that they did a bunch of things to talk about what cognitive function is in their population. Whether it was adequate or not is a different question. But they were really using DSST as a measure of change.

So I'm just trying to make sure we know why

we're discussing function versus change. And it may be a subtle thing, but I think it's important for thinking about what we're trying to figure out.

DR. PICKAR: Let's be -- we can turn that question back to our friends at FDA. Is indeed cognitive function what you wish to say?

DR. FARCHIONE: Well, yes. The claim that the sponsor is pursuing has to do with improvement in cognitive dysfunction, so an improvement in cognitive functioning more generally. And you're right, there are a bunch of other measures. But this was the prespecified primary endpoint in one of the studies, and then it was part of the primary measure. In the other study, it was the first prespecified secondary measure in that study as well.

So because that was where the statistics were focused, that's why we're asking it as the focus of this question.

DR. PICKAR: Dr. Grieger?

DR. TEMPLE: Before you leave that, it was also the principle thing that they looked for a

change in, so it was -- right. They looked at other things, too, but this is about this one.

DR. GRIEGER: Well, I think the question as it's written right there, the answer would be no. It's not -- we wouldn't do a one instrument assessment of somebody's cognitive function in clinical work. Is it a measure of a change of some aspects of cognitive function?

I mean, we're not even sure exactly what it covers. It covers executive function. It covers eye-hand coordination. It includes a bunch of different facets of cognition. But it doesn't include all of them. It's not an intelligence marker. There are a number of things it doesn't capture.

So I would say the simple answer to that is no, but if it was reworded to say a measure in change of cognitive function as a result of treatment, then I would say probably.

DR. PICKAR: Dr. Stein?

DR. STEIN: Rather than answer this yes or no, I think I'd say that given the circumstances

where the company was, a priori, trying to pick probably a single primary cognitive measure, this to me seems like, even in retrospect, that it was a good choice. And I say that because there's a fair bit of data on the DSST. It's pretty clear that it taps into domains that are very relevant to major depression. It probably doesn't cover everything, but by the same token, it's also sufficiently broad that it does cover the domains that are probably going to change and it has been shown to change with treatment.

So I think it's actually quite good as a single measure.

DR. PICKAR: Other comments? Dr. Mathis?

DR. MATHIS: Perhaps we overthought this when we wrote the question, but we wrote it as an adequate measure of cognitive function in MDD, and we specifically made it a discussion question instead of a voting question to have this discussion.

DR. PICKAR: I think that's right on. Yes?

DR. COMPAGNI PORTIS: Well, I would say that

I think it's an incomplete measure. And back to the conversations we had before, that there are a number of things that it doesn't take into account, whether that's processing speed -- I know that "adequate" word is hard. But I don't think it's an effective enough measure of what we want to look at here to make the kind of claim that the sponsors are wanting us to agree with.

DR. PICKAR: Dr. Portis, that's an important comment. Say it again, just so I have clarity.

DR. COMPAGNI PORTIS: I don't think that it is comprehensive enough to cover the kind of claim the sponsor wants to make, that based on this one measure, we can say that this drug is an adequate measure of cognitive function. And I think that it doesn't account for the other issues, such as processing speed and any other learning disabilities or any other prior issues that are preexisting issues.

DR. PICKAR: Raj, you're up?

DR. NARENDRAN: It seems -- I kind of feel split on this. On one hand, they picked this

measure, which taps into broad multiple domains, and they're using it -- they used it very successfully to demonstrate a pretty convergent data set that it changed. But on the other end, it seems like there's a lot of issues related to the unknown of the DSST, how well it relates to clinical outcome.

I thought your neurology consult that you guys got from the division was fabulous because I think -- and one of the things that they said is a pragmatic approach would be to probably allow them to include this data, but then acknowledge the ambivalence of what is unknown.

If you do that, I think it's probably reasonable to say -- but it's not really a hard and fast adequate measure per se, but I don't think they should be penalized for that because they did the best of what they could do. I was pretty impressed with that consultation the neurology people wrote.

DR. PICKAR: Dr. Farchione?

DR. FARCHIONE: I think, going back to

Mitch's point about how we may have overthought the question a little bit, perhaps -- and I don't know if I'm allowed to do this at this point. But like we were saying, the DSST, it was part of the primary in one. It was the sole primary in the other study.

There were a whole bunch of other tests that were part of these studies, too. When you take the data -- when you take all of that data in its totality and think, so maybe if that was just it on its own, it's probably not adequate. But now you've got all of these other things that probably overlap, maybe you support, maybe you don't support, depending on how you look at it.

In this context, in this study of this patient population, with all of these other measures that you have, does that sort of change your mind a little bit about whether or not they met the bar?

DR. PICKAR: Dr. Ionescu?

DR. IONESCU: Yes. I just wanted to agree with Raj a bit on what he just said, I think from

where we stand looking at this question, it did answer, a priori, what they set out to do. The question that still remains for me is, what are we really testing in cognitive function?

Is it really that patients are having a hard time with processing speed and executive function of filling in these symbols, or is their mind somewhere else thinking about something more negative, or that bias, that valence bias I was talking about earlier today? I think that's of course a different question, too. But I think just looking at this question as it's written, based on what the company did, I would say yes at this point.

DR. PICKAR: Dr. McMahon?

DR. McMAHON: Well, I'll take the license that I think we've been given to interpret the word "adequate" broadly. I think what I feel most comfortable saying is that I think it serves as a reasonable proxy measure compared to the 6 or 8-hour battery that any of us would do if we really wanted to look at this thoroughly.

So while I share the concern that it may be contaminated by mood changes, and I don't think that's been adequately addressed, I've been persuaded as a non-neuropsychologist but as someone who's interested in mood disorders that it serves as an adequate proxy of some ill-defined sense of cognitive disorder.

DR. PICKAR: I think in some ways that summarizes this part of the discussion. Adequate -- it ranges from an adequate to a measure, and not quite perfect, that I think you commented earlier. Dr. Portis, we're on target of being where -- it could fall short. But is a measure, as Dr. Stein pointed out.

Yes?

DR. HINKIN: Can I get a little clarification as to this question? Will this be just specific to this drug, or is this going to set some sort of policy for FDA coming down stream where Digit Symbol will be seen as adequate and sufficient?

DR. FARCHIONE: No. I don't think that we

have any intent of codifying this as the way to look at cognitive function. But the trouble that we run into is that a lot of times, once something lands in a label, then every other company looks at that as their instruction manual for how to move forward with their own development programs.

DR. PICKAR: Dr. Temple, you've had some experience in this sort of thing. What's your thought?

DR. TEMPLE: Well, you're saying using it in a label as implication, and there isn't any question that it is. I felt the proxy statement was very helpful. We know perfectly well -- everybody knows perfectly well that this does not measure all aspects of cognitive function; of course it doesn't. But the question was is it a reasonable measure that might be more broadly thought of, and I think your proxy description captured what we were interested in; is it a reasonable measure for cognitive function, even if it doesn't measure all of them, because we know it doesn't do that.

DR. PICKAR: I think that handles that question very nicely. Let's move on to number 2, which has been lurking around all our conversations this morning and so forth. What, if any, additional data are needed pre- or post-approval to address the outstanding issues? And be clear whether you believe these data should be required prior to approval. So there's a key issue.

Yes, Dr. Higgins?

DR. HIGGINS: Yes. I actually -- I have some real ideas of how the data could be improved over time. But I would propose that this be done post-approval. It's not required that it be done pre-, and I want to see longer term studies and more diverse populations like we heard from a public speaker today.

DR. PICKAR: Other comments? Ionescu?

DR. IONESCU: Thanks.

DR. PICKAR: How are you? Good.

DR. IONESCU: I was just going to agree with something that was said earlier today of having an anchor measure, and I do not believe this needs to

be done pre-approval, so post-approval would be fine; but sort of like an anchor measure, how is this related to the depression and anchoring it to what we know clinically as improvement.

DR. PICKAR: Dr. Grieger?

DR. GRIEGER: This is not directly related to the question at hand, but I don't see it listed in the other questions for discussion. But what does it mean to have the clinical trial referenced and the results of it, but not suggest that it's an indication? What does that mean? Does that mean you can advertise based on a clinical trial that occurred?

DR. PICKAR: On television as well?

DR. TEMPLE: Yes. It means you can basically promote these statements as part of your advertising.

DR. GRIEGER: Even though it's not an indication.

DR. TEMPLE: Even though it's not --

DR. GRIEGER: Because you look at the other drugs like Abilify, and it's got an indication for

this, indication for that, indication for another thing.

DR. TEMPLE: Whether to make it an indication has to do with whether you think it's part of depression but one particular thing, or whether you think it's a totally different claim, all of that kind of stuff. And you could come out in various places on that question.

DR. GRIEGER: That goes back to an symptom within a syndrome.

DR. TEMPLE: Yes.

DR. GRIEGER: If you're already approved for the syndrome, you don't need to have a specific approval for a symptom.

DR. TEMPLE: Right, even when you give something a claim for depression, you don't write in the indication section what it did on this item and the HAMD, and all that stuff.

DR. GRIEGER: Okay.

DR. PICKAR: I think our discussion is plenty of issues remaining. Do they need to be addressed pre- or post-approval? We certainly

heard one person say post-approval, and there's an important comment right there.

DR. UNGER: Thank you. I'm Ellis Unger. I'm director of Office of Drug Evaluation I. There is no pre- or post-approval here. I need to make that very clear. The drug is approved. It's on the market. So all we're talking about is whether the FDA would approve this supplement, which would put something in section 14 of the label that would say the DSST was better, cognitive function was better, which would enable the company to immediately advertise on TV, and wherever they advertise, this is the only drug that's been shown to improve cognitive function in depression.

So people need to understand that. People should think about -- the earlier question about is this a new paradigm for other drugs, does this mean that any new antidepressant could simply do a test, a DSST, during their development and get the same claim in this label? The same with other antidepressants.

But the question is -- we had some

difficulty earlier extricating the change in the DSST from the change in depression. So if someone comes along and they study depression and show depression's better and the DSST is better, do they get to put that in their label? This is something you all need to think about I think.

DR. PICKAR: I assume that would have to be a primary endpoint, then. Would that be correct?

DR. UNGER: Well, you win on the primary endpoint maybe, and then you make that a secondary endpoint. And there are ways to prospectively plan a study so that you can get more than one claim, yes.

DR. PICKAR: Dr. Higgins?

DR. HIGGINS: I don't mean to be a stickler, but the question is asking us about post- or pre-approval, and maybe the wording it was not chosen --

DR. FARCHIONE: We meant pre- or post-approval of this particular supplement.

DR. HIGGINS: Of a claim.

DR. FARCHIONE: So the drug itself is

approved, but it's this supplemental application where they're seeking this additional claim.

DR. HIGGINS: I see. So I stand by my original statement, then.

DR. PICKAR: Dr. Portis?

DR. COMPAGNI PORTIS: As we all agree I think and heard from very compelling speakers, the need is real, and people really do need something. I want to echo what you said about longer term studies and making a big claim that is going to go into advertising, and how does that impact other drugs, and what they do or don't do.

I would like to see more studies that compare, more comparative studies. I'd like to see that longer term data, and I'd like to see it include more functional measures, even though I know that also has challenges. But I think it's a really important piece because I go back to this question of what we're measuring. I mean, even some of the functional measures, you're talking about, a baseline that -- well, we don't know what the baseline is. And it's different from people.

How functional? We heard from speakers that really were functioning at a high level, and then we've got questions and things we're asking people to do that really don't speak to that challenge of what it really means to be impaired in your daily life.

DR. PICKAR: Dr. McMahon -- I'm sorry. Dr. McMahon first, and then Dr. Hinkin.

DR. McMAHON: I was just going to say that I would be uncomfortable with a statement that this is the only drug that improves cognitive dysfunction in depression when it's only been compared, as far as I know, to one other drug. So that would concern me.

But a lot of the other things would interest me such as longer term studies, more diverse things, how to separate the improvement in cognition from the improvement in mood. None of those would concern me before approval. But if approval means that people would be told this is the only drug that improves cognition in depression, I'm uncomfortable with that.

DR. TEMPLE: They can't say that because they don't know that. But what about the statement that we're the only drug that's been shown to improve it.

DR. McMAHON: That's -- I hear you.

DR. TEMPLE: No, they can't claim comparative data when there aren't any.

DR. PICKAR: Dr. Hinkin?

DR. HINKIN: Yes. I think we're running back into that pseudospecificity issue with the way this study is designed here in that we're showing that you treat their depression, and their get symptoms get better, to a rather small degree in terms of the DSST.

So again, I can just see the ads on the television saying this is the only drug that's been approved, or shown, or whatever, and I don't think that would be accurate. What I would like to see is some way of showing that specific effect on cognition over and above. Improvement in that I could see.

DR. PICKAR: Dr. Narendran?

DR. NARENDRAN: I do want to reiterate what the other speakers said. I think it's -- it definitely improves the DSST. We all feel comfortable with that. But when you're saying it's -- is that really cognitive function per se in depression? I don't think that's the case. I think if that's what you want to do, I think you have to -- they must be -- they must go back and probably look at some more specific aspects of cognition to enhance the data set before you allow them to do that, I would think.

So I don't know if you could just say the proxy -- as a proxy is a good term, but I don't think that necessarily means that it improves cognitive function in depression per se. I don't think it's that conclusive. So you would require them to maybe do more trials to demonstrate that, I would think.

DR. PICKAR: Dr. Stein?

DR. STEIN: I was just going to say -- I don't know exactly what the wording should say, and maybe saying it improves cognition is too broad.

But it's going to say something like that. The company's ability, then, to say that this drug has been the only antidepressant shown to improve cognition, or whatever term is used, would be in my mind fine because it would be true. It would be the only one that's been shown and the FDA would have looked at to say that it's true.

We have lots of parallels like that. I think back to is there more indications for SSRIs and SNRIs in anxiety disorders. And certain companies would have done the studies to show that it works for a particular anxiety disorder and others couldn't say that. Does that mean that others don't work? No.

So I'm comfortable with that, and I would assume that the company would be extremely responsible and conservative in how they disseminated that information so that they're not sort of saying two-thirds of everybody with depression has cognitive dysfunction, so all of those people need to obviously start with Brintellix. I'd hope that there would be something

a little more --

DR. PICKAR: From a label point of view, would you say something like it's been shown effectiveness for a measure of cognitive dysfunction in depression? Right now, I'm just saying treating cognitive dysfunction is a big thing. We all know that this isn't just -- this is part of it.

DR. FARCHIONE: I'm a little reluctant to get into the weeds on the exact language of labeling because it's going to be a negotiation process.

DR. PICKAR: That will be your problem.

DR. FARCHIONE: Yes.

DR. PICKAR: Dr. Conley?

DR. CONLEY: Well, back to the weeds.

(Laughter.)

DR. CONLEY: But that's the word because I think you can probably see -- but probably this is informative enough to you -- that this is what people are really tripping over quite a bit, that cognitive dysfunction is a pretty big term. And if

you're kind of giving that, it may be beyond where the data lies.

But getting what is a substantial evidence claim into section 14 might be a little bit different. It's new. They are cognitive symptoms, whatever you want to call them; is a real thing. But I do just want to underline that I think that's -- I'll say it for myself, but as the industry rep just as a general thing, I just worry about -- I mean, I understand your worry, but at the same time, I worry about over-generalizing that.

To a degree, sorry, it doesn't make your job easy, and I get that. But you do have to really fight about what a specific wording is I would say for something like this. And I hear that, but that's where I don't want to -- I know even your voting question is about cognitive dysfunction, which seems broad to me. But anyhow, that's my comment on that.

DR. PICKAR: Yes, Dr. Farchione?

DR. FARCHIONE: I guess to make it a little

bit more broad for the committee to think about, if you think that in this program and in these studies that they have shown something that's meaningful, then after listening to all of your feedback as far as, well, maybe it's not cognitive dysfunction as a whole, maybe it's these aspects, blah, blah, blah, blah, those are the kinds of things that we would then take back into our labeling negotiations and try to nuance the wording so that it really reflects the data more accurately. But in order to get to those negotiations, we need to decide is this meaningful, is this not meaningful.

DR. PICKAR: That's important feedback to the committee. Dr. Temple?

DR. TEMPLE: One of the things -- once we decided that cognitive function wasn't necessarily pseudospecific, we then agonized between two things. One, do you have to really show you're different from all the others in some way? Not an easy thing to do if they all have some small effect or something like that, and clearly not something that has been shown yet; or given that everybody

thinks that the cognitive function problem is a very important one that has not been adequately assessed, is it good enough to show that you have an effect on cognitive function even if you don't have any comparative data?

We spent a long time agonizing about that, and that's part of why it's here.

DR. PICKAR: Dr. Grieger, and then the sponsor. Dr. Grieger's been waiting, and he's such a patient guy. Let him make his comment, and then to you, sir.

DR. GRIEGER: Well, I think, again, as the sponsor indicated before, maybe just saying something like, on this test, which is a marker of this and that, it is shown to demonstrate improvement. So you're not saying it's all cognitive, it's on this specific thing, which is used as a proxy for this and that. It does better.

But I'm going to go back against what I said before. I do think you need to define the population a little bit in terms of what was the severity of the depression, what was the severity

of the cognitive functioning at baseline? Because we all know there are people out there who prescribe antidepressants for people with adjustment disorders, marital problems, whatever. They throw a drug at it because it's the easiest thing to get the patient out of their office.

Quite frankly, probably too many people with mild depression are being treated pharmacologically instead of psychotherapeutically; whereas we know that these drugs are very good for people with severe depression, they don't hold up as well with people with mild depression in terms of resolving whatever it is they're experiencing.

So I think some comment about show this degree of -- however you want to parse that, 20-point below normal rating on this test, or this rating on the depression scale, whatever defines this population, because these studies always work better in sick people.

DR. PICKAR: Sorry.

DR. PARKER: Sorry. Dr. Parker from Takeda. So I appreciate the difficulty that the committee's

having with this because this is a brand new area. And really what I want to say, to echo actually from FDA's standpoint, is we actually haven't had the opportunity to have a label discussion yet, so we really don't know what the appropriate language would be, from both sides, in terms of how we could craft something in terms of what would be best.

We have put forward some thoughts. We definitely recognize the effect that we're talking about on the DSST, to be clear. We understand that there could be appropriate caveats in terms of the specific domains of most interest or that the FDA felt would be the ones most relevant to what we've seen.

But I think going back to what Dr. Farchione said, really, from our standpoint, do you see this as real and meaningful? If you agree with that, I think we have two more months with the FDA, of fun times, discussing what the label ramifications might mean. So I think from the statistical standpoint, you've got the reel, and now it's just is this meaningful; because if not, the answer is

it won't be in the label. Patients and doctors won't know about it.

DR. PICKAR: Well, I think we all recognize that this is going to have a big impact on the practice of the field.

Dr. Dickinson?

DR. DICKINSON: So my comment actually goes directly t that point, and I think we've talked about whether there's some substantial evidence for a change in this measure and whether this measure is something that represents cognition broadly, or narrowly, or whatever. But what we haven't come back to, though, which we talked about earlier in the day, is that this is -- let's say it is substantial. It does seem to me that there's kind of a nice convergence of different bits and pieces of evidences here. But is it a big effect? No, it's not.

I'm not as convinced about the effect size data that was presented. It seems to me that you have pretty good evidence of a very modest effect on cognition, at least in this big sample approach,

to evaluating things.

I'm also really impressed that there are a number of people for whom cognitive impairment is a huge issue and who are really, really anxious to have options, and that we should think about that, too. But I don't think we've got evidence here of a big effect. I think we've got evidence of a relatively small effect.

DR. PICKAR: Indeed. And I want to move on to discussion of item 3. But on that, it is a modest effect. On the other hand, from a risk/reward benefit, there's not a lot of risk to it other than maybe, I don't know, in the clinical setting. Do people find any risk to this? What would be a risk to this in the clinical setting, in giving a drug that may or may not benefit? We do that in good faith all the time.

DR. DICKINSON: I'm not sure the risk is clinical. I think what we've talked about in the last 15 or 20 minutes is the risk that this impacts the way the industry kind of starts dealing with antidepressants, and does this now generate a rush

of 20 companies to test every little --

DR. PICKAR: That is a huge question. I'm not sure that's the charge -- maybe it is a question I didn't read yet that you want our opinion on, but I don't think so.

Dr. Stein?

DR. STEIN: I think there is some clinical risk. I kind of alluded to it earlier, where if physicians were to hear about this and start taking all of their patients with residual cognitive symptoms who were doing pretty well on their antidepressant, maybe not great, and saying everybody's got to now go over to vortioxetine, then that could be a problem.

It's important for us to remember that there are no data saying what happens when you switch people who have cognitive dysfunction on their current antidepressant to vortioxetine. There's no data that I'm aware of that showed that they do better, yet that is what will happen clinically. So I think there is some risk.

DR. PICKAR: Fair enough. Let me read

question 3. Let's just move towards that. Does a claim for an effect on cognitive function require showing of superiority to another antidepressant or more than one, or is it sufficient to show an effect versus placebo on cognitive function? Thoughts?

Dr. Stein?

DR. STEIN: Yes, I think it's sufficient to show that there's an effect on cognitive function. I don't think that there's a requirement that it be compared to something else when no antidepressants can say that probably.

DR. PICKAR: That's correct in my assessment, but maybe other people feel otherwise. Francis? Dr. McMahon?

DR. McMAHON: So if I understand this question correctly, though, it seems to me that if we were to say that superiority to placebo is sufficient, then we really do have no way of telling improvement in cognition from improvement in depression.

I found the data presented earlier today,

with at least one comparator drug, helpful in trying to sort that out. Without a comparator drug, then it really isn't possible to tell. We all agree that most people with depression have some degree of cognitive dysfunction and that many people when they improve, that improves as well. So without a comparator drug, I don't know how you'd sort that out.

DR. PICKAR: Well, we certainly have the two controlled studies that go in one way, but I must say I agree with you. Seeing that comparative study registered in the overall view of the data. Other thoughts? Dr. Temple?

DR. TEMPLE: Well, but in that study, it was not even nominally, significantly better than duloxetine. I mean, it leaned a little, but -- that's okay, that's good enough, that's the comparator that convinces you?

Remember -- I tried to pose this before -- everybody says that this has not been paid enough attention to, that this is an important part of the depression syndrome, hasn't really been

well studied but is often there. So that thought really is asking the question, if you've now gone and studied something that nobody ever bothered to do before and showed that it's part of the response to the antidepressant, is that good enough by itself, even if it might be true that other drugs studied could also do the same thing? They just haven't studied it. That's what that question's about.

DR. PICKAR: Right. Right. Dr. McMahon, do you have any other comment?

DR. McMAHON: Well, I imagine it's true that no direct comparison was made between the duloxetine and the vortioxetine in these studies. It was really --

DR. TEMPLE: It was. They were both there, but you can see they're not significantly different.

DR. McMAHON: Yes.

DR. FARCHIONE: And I will say that we dig into that data. It wasn't part of it, but we did look at the comparison and change from the

vortioxetine group versus the duloxetine group. And those two, even though vortioxetine beat placebo, duloxetine did not beat placebo. Vortioxetine didn't statistically beat duloxetine.

DR. McMAHON: Right. I understand that data. I imagine there are design and power issues that would get involved in those kind of direct comparisons. It would be a study I'd like to see at some point. I'd like to see it compared to lots of antidepressants, but I don't think it's essential to being able to say that this is improving cognition to some degree.

DR. PICKAR: Dr. Narendran?

DR. NARENDRAN: I do want to support the idea that I think it's -- I mean, to try and tease out if this a mood disorder related effect, antidepressant effect versus is this a cognitive disorder effect when major depression itself is just a cluster of symptoms, and it's not really based in biology -- so I think that's more an academic exercise. If it beats placebo and cognition improves, I think it's okay. It's

reasonable. To have a comparator as they did I think is commendable, but I don't think that in itself should guide the decision process per se.

DR. PICKAR: Dr. Conley?

DR. CONLEY: So this goes back to this and maybe what -- I know you entered into a lot of negotiations as this process goes along, and I'm not sure -- I just don't remember -- it may have been in the briefing document -- of what you said about this. Was this okay with you as a trial design, with basically showing superiority to placebo? But in essence, I think -- I saw -- I was reading that duloxetine in there is basically just an active control, not really a true comparator. It wasn't powered for that I don't think.

DR. FARCHIONE: And that's really what I was trying to say when I gave that brief overview on the regulatory issue.

DR. CONLEY: That's what I thought.

DR. FARCHIONE: So we didn't really have a whole lot of input because we were approaching it from the perspective that this was pseudospecific,

and we weren't really going to entertain it anyway.

DR. CONLEY: Got it. So it wasn't as if there -- obviously, you didn't have a SPA about this. But that helps. I just didn't understand that. But I do think the sponsor didn't power it to be separating the two.

DR. PICKAR: Right.

DR. TEMPLE: You know, there's language in some of the early descriptions of the study that suggest that they hope they would beat it. But you're right. If it has a little effect but not as big effect, your chances of winning are sort of small.

DR. CONLEY: Yes. And I mean part of the worry I have about this, as we've all talked about, the fact that people who have depression often have some cognitive manifestations of that -- I'm trying to figure out a term for that -- that get better as their depression gets better. So that's whole worry about pseudospecificity, of course. But that means that every antidepressant, every depression therapy is going to show a little bit of something,

and that's going to make it harder to separate anything that's even real.

DR. TEMPLE: In thinking about this, one other possibility, not that it's been done, is to take people with a pretty good response on their overall depression but who have residual cognitive dysfunction, and either do an add-on study, or a substitute study, or something like that, and show that you do better. That hasn't been done yet, but that's an enrichment design that could show it if it's true. If they're really better than the other drugs, it would come out in that kind of study. But we did not insist on that in any way.

DR. CONLEY: And you all presented it correctly that -- I mean, in some ways I'd say you can plan the future pretty well, but unfortunately you have to deal with the present, that you do have this application in the middle of trying to think through that. I've heard that, too.

DR. PICKAR: Okay. Just summarizing question 3, does it require showing superiority to another antidepressant. I think the general

question was no, but, boy, it's interesting to see it, and we're all going to look forward to it. I think we're going to be reading a lot of these studies going forward. It just has that feeling to me. The feedback to you is it's not limiting, but it will be interesting, and we'll probably have that interest down the road. We'll see it all.

Other comments before we move on to the fourth question, which is a voting question. Other comments before we go to vote?

(No response.)

DR. PICKAR: Okay. Let me read the vote out loud. Has substantial evidence been presented by the applicant to support a claim of effectiveness for vortioxetine for treatment of cognitive dysfunction in major depressive disorder? That's the question that we go.

We move on here now, and I think we're supposed to see buttons on our microphone. There we go. Do you see them blinking? What you do is you just start doing it, yes, no, abstain. You have about 20 seconds to do it. Press the button

firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

DR. TEMPLE: Could I just say one thing?

DR. PICKAR: Sure.

DR. TEMPLE: There's been some discussion about whether this is a measure of cognitive function in toto or something like that. This question is really about whether they've shown an effect on some aspect of cognitive function, however you turn to describe it later.

DR. PICKAR: That's exactly right. We were getting into big questions --

DR. TEMPLE: Yes.

DR. PICKAR: -- and interesting conversation, but this is much more specific than that, and it's around the data that was shown. And I think when you vote, you focus on that, and that's the way this process works, is you keep score. The data's been shown, and now your opinion

about it.

We can go around the room to discuss and then do the votes if you'd like to. We can do it quickly. You don't have to say anything. Dr. Conley, anything more?

DR. CONLEY: No. I appreciate the clarification of it, not being as broad, being a little more specific. That seems great.

DR. PICKAR: Anybody else want to comment? I think we go ahead and vote, then we speak about the vote afterwards. I think that's the way it's done. Correct? Okay, folks. Here we go. Are we ready over there? Thank you.

(Vote taken.)

MS. BHATT: So the voting results, yes is 8; no is 2; abstain, zero.

DR. PICKAR: We have here is the actual recording of how we all voted, and we're going to around the table, which is the tradition, and just say a comment, you don't have to say anything more, just to confirm your vote. If you have a comment, but all means share it.

So let's start down there. Dr. Conley, you didn't vote, so Dr. Dickinson.

DR. DICKINSON: I guess I voted yes. And my comment is that I think in the totality, not just the Digit Symbol data but also the data with respect to other cognitive measures, and additionally the data with respect to the UPSA, which I kind of think of as a cognitive measure, that there's evidence of a small effect.

DR. HINKIN: I voted no because I did not see in the data a substantial effect, part of that prong of the statement. Yes, some minor small negligible, but not substantial.

DR. PICKAR: Would you declare you name? Because this is a formal vote. I didn't ask you to do that.

DR. HINKIN: Dr. Charles Hinkin.

DR. PICKAR: And Dwight? I'd like to make sure you know who you are.

(Laughter.)

DR. DICKINSON: Dr. Dwight Dickinson.

DR. PICKAR: Nice job. Okay. Dr. McMahon?

DR. McMAHON: Dr. Francis McMahon. I was persuaded to vote yes by the preponderance of the evidence and the big clinical need to address all aspects of impairment in depression, and the problems we have with currently available treatments in doing that.

DR. COMPAGNI PORTIS: Natalie Compagni Portis. I voted no because of the -- as it was stated, that I didn't feel like there was substantial evidence. I think there's an important need, and I feel like there's some real excitement about the possibility here. But I feel like the information is limited and the brevity of the data and the small effect size is concerning to me.

DR. HIGGINS: Jennifer Higgins. Based on my consideration of all the data, I voted yes.

DR. GRIEGER: Thomas Grieger. I voted yes. I think it's like all medications. We'll know in the long run whether it's that much better or not at all different. But this gives -- at least it gives clinicians a thought of something different to do than what they might be doing already with a

patient who isn't getting well.

DR. PICKAR: David Pickar. I voted yes, and I agree with the comments, favorable comments. And to the FDA to work on completing this, this is going to make a difference in practice.

DR. IONESCU: Dawn Ionescu. I voted yes. I voted this based on the data that was presented today. The only question that remains in my mind after the discussion today is what is the brain doing when it's not concentrating on these tasks in our patients with depression?

DR. STEIN: Murray Stein. I voted yes. I was thinking about what we would expect the company to do if they'd done these studies and showed that their drug works in cognition, and I think we'd expect them to put it in the label. So they've done the studies. They've shown that there's been some improvement. It's not huge, but it's better than placebo, and I think it belongs in the label.

DR. NARENDRAN: Raj Narendran. I voted yes as well. I think I overall thought that the data was pretty convergent and conclusive that it does

have an effect, though the magnitude of the effect is still under question and the clinical relevance is still under question. But it seems to be -- I don't think anything more or less is going to add to it at this point.

Adjournment

DR. PICKAR: Well, thank you very much. And, Kalyani Bhatt, thank you very much for helping us through this. Unless there are any more questions or comments, we will adjourn the meeting. I hope it's helpful to our FDA colleagues. And take your stuff with you. All materials left on the table will be disposed of I am told.

Thank you all very much. Thank you for coming.

(Whereupon, at 4:36 p.m., the afternoon session was adjourned.)