UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

+ + +

March 21, 2019
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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|---|---|
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| ELIJAH WREH, M.S. | Industry Representative |
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| ADEN S. ASEFA, M.P.H. | Designated Federal Officer |

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M E E T I N G

(8:02 a.m.)

DR. JENSEN: Good morning. If everybody could take their seats, please, I would like to call this meeting of the Neurological Devices Panel to order. I am Dr. Mary Jensen. I'm the chairperson of this Panel. I am an interventional nerve radiologist at the University of Virginia and a professor of neurology, radiology, and neurosurgery.

UNIDENTIFIED SPEAKERS: We can't hear.

DR. JENSEN: You can't hear me?

UNIDENTIFIED SPEAKER: No.

DR. JENSEN: Oh, okay. How's this? Is that better? If I eat the microphone? All right, good.

So I'd like to first introduce the Panel to our participants. And I'd like to start over here with Dr. Pena.

DR. PENA: Hi. Good morning. Carlos Pena, Director for the review division of Neurological and Physical -- this is not working.

DR. JENSEN: No.

DR. PENA: Devices, at the Center for Devices, FDA.

DR. JAIN: Filipe -- that, Dr. Filipe Jain, Assistant Professor of Psychiatry at Harvard Medical School.

DR. ROSENBERG: Paul Rosenberg, Professor of Psychiatry at Johns Hopkins University School of Medicine.

DR. PROSCHAN: Michael Proschan. I'm a mathematical statistician at the National Institute of Allergy and Infectious Diseases.

DR. BELL: Karen Bell, Professor of Neurology at Columbia University Medical Center.

DR. POSTMA: Hey, Terri Postma. I'm a neurologist. I work at the Centers for

Medicare and Medicaid Services.

DR. KNOPMAN: My name is Dave Knopman. I'm a behavioral neurologist in Mayo Clinic in Rochester, Minnesota, a Professor of Neurology.

DR. GOODMAN: Wayne Goodman. I'm a psychiatrist and Chair of the Department of the Psychiatry at Baylor College of Medicine in Houston, Texas.

DR. DORSEY: Good morning. My name is Ray Dorsey. I'm a neurologist at the University of Rochester.

MS. ASEFA: Good morning. Aden Asefa, Designated Federal Officer for this meeting.

DR. PILITSIS: Julie Pilitsis, Professor of Neurosurgery, Albany Medical College, Chair of the Department of Neuroscience.

DR. BAXTER: Blaise Baxter. I'm a Chair of Radiology, University of Tennessee, Chattanooga.

DR. JOHNSTON: Good morning. Karen Johnston, Professor of Neurology, University of Virginia.

DR. ELLENBERG: Good morning. Jonas Ellenberg, Professor of Biostatistics, University of Pennsylvania Medical School.

DR. ANDERSON: Karen Anderson, psychiatrist, Georgetown University.

DR. LYDEN: Pat Lyden, Professor of Neurology at Cedars-Sinai Medical Center in Los Angeles.

DR. DUFF: Kevin Duff, neuropsychologist, Professor of Neurology at the University of Utah.

MS. EDWARDS: Veverly Edwards, Consumer Rep., Memphis, Tennessee.

MR. TAYLOR: James Taylor, Patient Representative, New York City, New York.

MR. WREH: Good morning. I'm Elijah Wreh, Industry Rep., Elyria, Ohio.

DR. JENSEN: I note for the record that the voting members present constitute a

quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

Before we begin, I would like to ask our distinguished panel members, which I've already done, and FDA staff seated at this table to introduce themselves. And Dr. Pena has done that. Sorry I got ahead of myself. If you have not already done so, please sign the attendance sheets that are on the table by the doors.

Ms. Asefa, the Designated Federal Officer for the Neurological Devices Panel, will now make some introductory remarks.

MS. ASEFA: Good morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration (FDA) is convening today's meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel 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 Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened

for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses, minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations on clinical information related to the de novo request for the neuroAD Therapy System by Neuronix, Limited. The neuroAD Therapy System is intended to provide concurrent neurostimulation and cognitive training for the treatment of mild to moderate Alzheimer's dementia.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict-of-interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Elijah Wreh is serving as our Industry Representative, acting on behalf of all industry, and is employed by Invacare Corporation.

We would like to remind members and consultants 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 the participants to advise the Panel of any financial relationships they may have with any firm at issue.

A copy of this statement will be available for review at the registration table during the meeting and will be included as part of the official transcript.

For the duration of the Neurological Devices Panel Meeting on March 21st, 2019, Drs. Felipe Jain, David Knopman, and Michael Proschan have been appointed to serve as Temporary Non-Voting Members, and Mr. James Taylor has been appointed to serve as

Temporary Non-Voting Patient Representative.

For the record, Dr. Jain serves as a member to the Psychopharmacological Drug Advisory Committee in the Center for Drug Evaluation and Research (CDER). Dr. Knopman serves as a member to the Peripheral and Central Nervous System Drugs Advisory Committee in CDER, and Dr. Proschan serves as a regular Government employee to the Endocrinologic and Metabolic Drug Advisory Committee in CDER.

These individuals are special Government employees or regular Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

The appointments were authorized by Russell Fortney, Director of Advisory Committee Oversight and Management Staff in the Office of Special Medical Programs, on March 19th, 2019.

A copy of this statement will be available for review at the registration table during the meeting and will be included as part of the official transcript.

Thank you.

Before I turn the meeting over to the Chair, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Stephanie Caccomo. If anyone from the press desire to speak to her, please see Mr. Artair Mallet at the desk outside the meeting room to obtain her contact information.

I would like to remind everyone that members of the public and press are not

permitted to the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until the Panel meeting has concluded.

And if you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide, please arrange to do so with Mr. Artair Mallett at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

And, finally, please silence your cell phones and all other electronic devices at this time.

Thank you, and I will now turn over the meeting to the Chair.

DR. JENSEN: Thank you.

We will now proceed to FDA's introduction. I would like to invite Dr. Pena to approach the podium, or if he would like to stay at his seat, that's fine also. I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the chair.

DR. PENA: Thank you, Dr. Jensen.

Good morning, attendees for today's meeting and panel members. On behalf of FDA, I would also like to welcome you to today's Neurological Devices Advisory Committee meeting. Alzheimer's disease is important to FDA. Patients with Alzheimer's disease are important to FDA. And ensuring patients in the U.S. have access to high quality, safe, and effective medical devices of public health importance first in the world is also important to FDA.

The public trusts us and our decisions in making sure all medical devices that are accessible in the U.S. have a reasonable assurance of safety and effectiveness, and we hope you all are as smart as we think you are in helping us with the review and the discussion

today, and we look forward to the meeting. Thank you.

DR. JENSEN: Thank you very much.

We will now proceed to the Sponsor's presentation. I would like to invite the Sponsor to approach the podium. I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel chair. The Sponsor will have 90 minutes to present. You may now begin your presentation.

MR. BAROR: Good morning, everyone. My name is Eyal Baror. I'm the CEO and President of Neuronix.

I would like to start by thanking FDA and panel members for their time and efforts in reviewing our de novo application for the clearance of neuroAD Therapy System for the treatment of mild to moderate Alzheimer's disease.

As of our agenda for today, after I make a short introduction of Neuronix, we will hear about the guidelines related to the de novo clearance pathway. We will then move to a discussion on Alzheimer's disease and transcranial magnetic stimulation, obviously followed by a description of the neuroAD Therapy System and how it works. We will then move to the focus of our presentation, the clinical data. We will start with the main body of the evidence, which is the U.S. pivotal study results, and then move to present data of supportive and confirmatory studies that we have gathered over the years. We will then proceed to discuss the clinical significance of the results that we have shown, and we will finally conclude with perspectives of our researchers and physicians.

Our main speakers for today: Dr. Alvaro Pascual-Leone, Professor of Neurology and Associate Dean for Clinical and Translational Science, Harvard Medical School; Dr. Marwan Sabbath, Director, Cleveland Clinic Lou Ruvo Center for Brain Health; Dr. Lon Schneider, Professor of Psychiatry, Neurology and Gerontology, University of Southern California;

Dr. Susan Alpert, former Director, Office of Device Evaluation in FDA; Dr. Phil Lavin, former FDA statistical consultant; and Moran Ploznik, Neuronix VP, Clinical and Regulatory Affairs.

Additional speakers we have with us today: Dr. Marc Agronin, Associate Professor of Psychiatry and Neurology, University of Miami; Dr. Babak Tousi, head of Clinical Trials Program, Cleveland Clinic in Cleveland; and Dr. Stella Karantzoulis, former Assistant Professor of Neurology in Langone Medical Center, NYU.

A few words about the company: So Neuronix was established back in 2008. We are obviously focusing on development of medical device technology for treatment of dementia, in particular, dementia of the Alzheimer's type. Our first immense study was performed, started 10 years ago in the summer of 2009. And since then, we have concluded over a dozen other clinical studies in different countries. Thirteen of these studies support this FDA submission. All of the studies have either been published or were submitted for publication.

We have been awarded the European conformity mark, CE, back in 2012, and following this we have been commercially approved for use in the European Union countries, in Australia, and also obviously in Israel. In the EU and in Israel, we are confirmed and approved to use for treatment of mild to moderate AD. In Australia we received the approval back in 2017, and the indication was mild to moderate AD with baseline ADAS-Cog of up to 30, which is exactly the indication that we are here discussing today.

All in all, the system is currently commercially available in clinics around the world, and as you will hear later on in the presentation, over 400 patients have been treated with the system, in different countries, in different settings, all with positive findings, both from randomized control studies as well as from real-world clinical data.

Our proposed indications for use are the discussion today. So the neuroAD Therapy

System is intended for neurostimulation concurrently combined with cognitive training. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type in patients with baseline ADAS-Cog of up to 30. And the neuroAD Therapy System may be used in conjunction with other pharmacological and non-pharmacological therapies.

And now I would like to discuss and present something of the overview of what we're going to show you in terms of the clinical data. As you all know by now, the pivotal study that we have run, the U.S. pivotal study did not meet its primary prespecified endpoint at 7 weeks. However, as you will hear over the coming hour and a half, we believe that there is ample evidence showing the following: one, that the neuroAD is consistently shown to be safe treatment, and that the device is extremely safe, that there is a clinically well-defined group of patients who show meaningful clinical benefits -- and please note that that group, as you will hear later on, represents 85% of the study cohort -- that the benefit is demonstrated on both cognitive and functional endpoints. And we have used the standard of scales in the industry, ADAS-Cog, for the cognitive evaluation and ADCS-CGIC for the functional evaluation.

And, moreover, the U.S. pivotal study findings are supported and confirmed by two independent Korean studies which had very similar protocols. And on top of that, as you will hear, 10 other smaller studies that were conducted always show the same trend of positive clinical outcome.

Maybe most importantly, the benefits that we show in our studies are on top of the standard, the current standard of care, and 80% of the patients that have participated in the different programs are already medicated for AD with cholinesterase inhibitors.

As you will hear later on from a physician who took the trouble to travel all the way from Europe and Australia to testify, the neuroAD system is already helping patients to improve their quality of life in the real clinical settings. We therefore believe that the

probable benefits of the neuroAD system outweigh the probable risks, and thus meeting the standard of the de novo clearance that is required. And this will be further explained by Dr. Susan Alpert.

So I'd like now to introduce Dr. Susan Alpert, former head of device, Office of Device Evaluation, to explain the de novo pathway and risk-benefit standards for clearance.

Dr. Alpert.

DR. ALPERT: Thank you.

Good morning. My name is Dr. Susan Alpert. As you heard, I am a previous Director of the Office of Device Evaluation. I held that position from '93 to '99. I also was the Senior Vice President for Global Regulatory Affairs for Medtronic. I'm a paid consultant to Neuronix. I don't hold any equity in the company, and I have no financial interest in the results of this meeting.

What I'd like to do in the next couple of minutes is just talk about the context in which we're here discussing neuroAD.

First of all, as we all know, this is an unmet need. And as you know from the materials that were provided to you, FDA has recognized that this novel therapy is a breakthrough. The product was originally in the Expedited Access pathway, which is now called Breakthrough, because this product meets unmet needs for irreversible, debilitating, and potentially fatal diseases like Alzheimer's. And the Breakthrough program is intended to move these products into the market more quickly than otherwise might happen.

So FDA therefore allows more uncertainty at the time of market entry, balanced with additional and continued data collection in the postmarket period so that we can continue to gather information to more completely understand the benefits and the risks of these breakthrough therapies but make them available as soon as possible, as soon as appropriate for the population.

What I'd like to talk about now for a couple of minutes is the de novo pathway. This product is first of a kind, although as you know, TMS is in the market. The combination of TMS and cognitive training is first of its kind for the treatment of Alzheimer's dementia. Because there's nothing in the market yet with this claim for Alzheimer's disease, the commonly used 510(k) pathway is not available for neuroAD. So it needs a new category, a de novo category.

The neuroAD, as you'll hear, is of low to moderate risk and has benefits. Those types of products have access to the market through this de novo pathway. We created the de novo pathway in the 1990s, when I was Director of ODE, for low to moderate risk products that could move more quickly into the market and not have to wait and go through the rigors of the extensive time for a PMA product, which is used for high-risk products.

Due to the lower risk category, the threshold for de novo is slightly different. It is probable benefits outweigh probable risks, so the high levels of statistical confidence that are used in PMA are not necessarily needed for these products. The benefits, however, as you heard from Dr. Pena, do need to outweigh the risks for de novo products, as they do for all products entering the U.S. market.

We believe that neuroAD has met this threshold, which is why we're here speaking to you today, that the probable benefits of the cognitive improvement that was achieved in the studies that you will hear about today outweigh the probable risks of this therapy in this population. So we believe the regulatory standard has been met, and that's why we're here speaking to you today.

Again, why do we believe we've met that standard? The risks for the TMS and the cognitive treatment -- cognitive training, sorry, for these patients are low. Although the changes, the benefits that we anticipated seeing at 7 weeks when the study was designed, the primary endpoint, was missed, by the 12-week secondary endpoint, real, measurable

benefit was demonstrated in a significant portion of the affected population. And as you've heard, these benefits are in addition to the standard of care therapies that 80% of the patients in the study were on. They were on standard, stable Alzheimer's medication, and they achieved these benefits on top of the benefits that they received from the medication.

Importantly, as you've heard, for de novo, the benefits and risks need to be in proportion, so the probable benefits, the benefits that you'll hear about outweighing the probable risks.

Finally, any remaining concerns that still exist at this stage are best answered in a carefully designed postmarket surveillance study, as a special control, something that's possible to be done in the de novo pathway, which is the most appropriate way to continue to gather this type of information in a broader population.

There are some additional considerations. We'd like you to keep these in mind as well as we deliberate today. First, FDA, as part of its strategic priorities, has acknowledged that it's very important to listen to the voice of the patient, to think about patient-centric outcomes for the treatment of different diseases. And as you'll hear later today in the Open Public Hearing, the patients have a voice here, as do their caregivers, something extremely important in the care of Alzheimer's dementia patients.

Secondly, as you saw in the briefing documents, a survey was done of 200 clinicians who care for Alzheimer's dementia patients on a regular basis to understand what does the clinical community expect of new therapies? And you'll hear that discussed more, and we're happy to share more information about that survey if you have questions.

Thirdly, FDA has the authority to understand the magnitude of benefits and risks for different types of therapies, considering how a device will be used. And, again, I remind you that this therapy is an adjunct. It does not replace current Alzheimer's treatments but is in addition to those treatments.

A group of researchers, a group called Researchers Against Alzheimer's, has raised some concerns about how these products are currently evaluated. And I'd like to quote from their open letter to FDA, again, putting context, this adjunctive therapy and how it should be thought about.

I quote, "If the FDA were to reject individually several safe and well-tolerated therapies with complementary mechanisms of action that each demonstrate a modest clinical benefit, it would unwittingly deprive patients of potentially substantial advances in the quality of treatment over the long run, with a combination of therapies. Most researchers believe that the future of Alzheimer's disease treatment lies in combination therapy." Again, it's important to remember that 80% of the subjects in the pivotal study were on stable Alzheimer's medications at the time of the study.

With that as a context for the discussion, I'd like to now turn the podium over to Dr. Pascual-Leone to talk about the data and the therapy itself.

DR. PASCUAL-LEONE: Thank you very much, Dr. Alpert.

And I would like to thank the FDA and this Panel for the opportunity of talking to you today. I'm Alvaro Pascual-Leone. I'm a Professor of Neurology and the Associate Dean for Clinical and Translational Research at Harvard Medical School. I serve also as the Director of the Berenson-Allen Center, which is a center dedicated to the development and translation to humans of noninvasive brain stimulation techniques and is broadly considered the international leader or one of the leaders in the development of these technologies.

I'm a cognitive behavioral neurologist, and my clinical practice is focused on taking care of patients with dementia, including Alzheimer's disease. And so this is a topic and a technology that is close to my heart and expertise and interest. And I was privileged to serve as a site PI for the U.S. pivotal study and welcome the opportunity to present to you

today.

I'm being compensated for my time and travel. I have no interest in the company. I own no shares. I don't expect to be, receive any direct benefit from the outcome of this meeting.

What I'd like to do today, to get us started is remind us of the unmet need in Alzheimer's disease and give you some background about the technology of the neuroAD methodology.

As you all know, Alzheimer's disease is a significant challenge for patients, their families, and our society. Nearly 6 million people are living with Alzheimer's disease in the U.S. alone. It is the third leading cause of death. It is increasing in prevalence and incidence, linked to the increasing lifespan of humans, thanks to the advances of medicine and public health. Unfortunately, despite this growing burden, there are to date no disease-modifying or preventative treatments, and there is a limited number of options for helping the patient cope with their cognitive challenges and disabilities.

Only two classes of medications, cholinesterase inhibitors and NMDA inhibitors have been approved. They can help patients, but unfortunately, oftentimes the patients develop side effects, and the efficacy of these medications is somewhat limited in magnitude and in duration. And so there is a need for additional interventions that may add on a benefit or extend the benefit of these patients.

Not surprisingly, pharmaceutical and other medical industries have developed pipelines and devoted significant effort to this challenge. However, more than 400 compounds have been tested and failed, and there's been no new drugs or interventions approved for the past 20 years. And the reason for that is because there have been no conclusive evidence that any of those interventions really showed a measurable benefit over a placebo.

As we think about how to help the patients, how to minimize their cognitive and behavioral problems, there is growing interest in the concept of multimodal treatments, combining different interventions, that might allow for reaching different targets through different mechanisms of action. And as you heard from Dr. Alpert, that would offer an opportunity to have greater impact on the disease and the disability that it causes. Of course, each one of the interventions ought to have measurable effect, or at the very least have a very favorable safety profile compared to the efficacy in order to proceed.

I hope that we'll be able to show you that the neuroAD system actually meets that. It is a fully integrated therapy that combines TMS with computerized cognitive training. It should not be thought of as TMS on the one hand and then cognitive training on the other. It is really the integrated combination that is critical. The notion is that the TMS target specific brain networks, modulates their level of activity, and through that targeted area, affects specific brain networks, enhancing their plasticity beyond the duration of the short burst of stimulation, and in doing so, opens a window of opportunity for the cognitive training to engage these same prime networks, leads thus to an enhanced benefit of the cognitive training, to an enhanced learning.

It is therefore the combination of both that is critical, and that combination, because of the mechanism of action, takes time to consolidate, consolidates over time, and leads to potentially a growing benefit, even after the intervention itself is completed.

Transcranial magnetic stimulation itself, as you heard from Dr. Alpert briefly, has been used and is in clinical use worldwide for a number of years. It is a noninvasive brain stimulation technique based on electromagnetic induction. Current passes through a coil, generates a magnetic field, and that induces a current in the brain.

Because of the possibility of neuronavigation, it is possible to target specific brain areas selectively. Several devices have been cleared by the FDA for major depression,

migraine, and obsessive-compulsive disorder. It is now covered by insurance, covered by Medicare, in widespread use in the U.S., and helping patients cope with major depressive disorder and medication refractory disorders worldwide.

In parallel to this clinical implementation, the International Federation of Clinical Neurophysiology, for the past 20 years, has had a consensus group reviewing the clinical evidence and the safety of this technique. I've had the honor to serve on the steering committee of this. There is a small risk of seizures that can be prevented when appropriate guidelines are followed. The overall side effect profile is quite benign, relatively mild, transient side effects. And importantly for the conversation today, this safety profile has also been demonstrated for an elderly population in the age range that we're going to be talking about.

This slide gives you an overview of the various devices that have been cleared by the FDA for TMS, starting in 2008 with the NeuroStar TMS System, that was reviewed by this very Panel and eventually approved for the treatment of major depressive disorder. It had failed the initial trial, but a specific group of patients could be identified that stood to benefit from the intervention for whom there is really no other alternative treatment at the time or even now.

Since then, a number of other devices have been cleared, and the applications have continued to evolve, improving on the protocols of stimulation and increasing the efficacy of the intervention. And as I mentioned, it is now being reimbursed and in broad clinical use.

On the right side of this slide, you have the BrainsWay Deep Transcranial Magnetic Stimulation System, recently approved in 2018 for OCD. And I want to highlight that one because it was the first intervention where TMS was combined with a behavioral intervention. It is the combination that led to the beneficial effect and ultimately to the

approval. It is going to be helping patients with a disabling disease.

I want to also use that study to highlight the fact that contrary to what is commonly seen in pharmaceutical studies, device-based studies have a much smaller *n* normally. This one, the BrainsWay study was approved with an *n* of 100, with a randomization of 1 to 1. And that is the case for the other approvals of TMS devices as well, given the type of process that device-based interventions go through.

The neuroAD system itself, therefore, because of the integration of cognitive training and TMS, combines a touch screen in front of the patient's chair, where the cognitive tasks are presented and where the participant responds to the tests, and a TMS system, where the coil is held over the subject's head and where the placement of the coil is guided by a neuronavigation system. The neuronavigation system is informed by the patient's own brain MRI. And, therefore, prior to the intervention, the patient undergoes a structural MRI scan.

Six anatomical regions are identified on that MRI, and guided placement of the coil is then implemented to ensure appropriate targeting. The six regions include language areas, prefrontal regions for executive function, and parietal cortex, targeting visual-spatial abilities. And targeting of those regions is then coupled with specific cognitive training that is designed to engage the same networks.

Each treatment session includes three alternate spatially discrete regions being targeted. And the reason not to target all six areas in each session is to make sure that the parameters of stimulation procession are within the safety guidelines currently recommended, both in terms of number of pulses, frequency of the stimulation, and the intensity. Overall, the protocol has five daily sessions of about an hour per week, for a total of 30 sessions over 6 weeks. And the intensity of the stimulation is set every day on the basis of the patient's motor threshold, as determined by the silent procedure

recommended by the International Federation of Clinical Neurophysiology and again to ensure the safety of the intervention.

So that what the subject actually goes through is summarized in this schematic. There is a brief burst of TMS to a specific brain region that maps onto the cognitive training that the subject then engages in. The subject responds to the given task, and then a new pulse of stimulation is applied to the same area, or when appropriate to a different area, with the appropriately coupled cognitive training.

After this brief introduction of the device and protocol, we like to start to focus on the clinical evidence. And as you heard from Dr. Baror already, there is a number of sources of data. We'll focus on the U.S. pivotal study, and Dr. Marwan Sabbagh and myself will try to share the details of that with you and highlight some of the aspects that you already are aware of. But there's really an addition of a number of other clinical trials by different groups that are independent of the company and that we believe provide valuable supporting and confirmatory evidence to the results of the pivotal study, and we'd like to review some of those with you as well.

In addition to that, because the device is approved in Europe and Australia and in Israel, there is a case series from clinical experience that have been published and provide further confirmatory evidence.

So, in total, there is 374 subjects overall. And if you look at the sources of these different ones, of course they have different weight in significance, but overall, they present a consistent and we believe robust body of evidence supporting the safety and the efficacy of the intervention for specific patients.

To start with the U.S. pivotal study then, let me briefly review the design first. As you all know, it was a prospective double-blind sham control study. Because the neuroAD intervention is the integrated TMS and computerized cognitive training intervention, that

was the active intervention, and the sham was the sham stimulation with "sham" in quotes, cognitive training, meaning really that the subjects were presented with stimuli on a computer screen and responded to them by touching the screen just as the real cognitive training, except these were not cognitive tasks but visual perceptual tasks, where they had to say whether they liked or disliked a given picture or a brief video of a movie.

The study was designed in consultation with the FDA, and the focus was on acute effect, not on durability of the effects but on acute effects of the intervention. And the decision, as you will hear later, was made to set the acute effect on a metric that had both an immediately after the intervention at 7 weeks' time point and a slightly later time point because of the possibility of these effects beyond the duration of the intervention itself at 12 weeks.

It was a multi-center study, with nine sites in the U.S., one site in Israel. It was focused on mild to moderate patients with dementia due to Alzheimer's disease, diagnosed on clinical grounds. At the time, PET studies and other biomarkers were not yet really established as an indication of diagnosis in trials.

It was a 12-week study, 6 weeks of the intervention and then that 6 week of, quote, "follow-up," again focused on the acute effects. Great care was taken in blinding the subjects as well as their caregivers, also the investigators and the raters, with two different raters being responsible for the ADAS-Cog and the CGIC as the two main outcome measures. The only person that was unblinded was the technician applying the stimulation to the patients.

Each side, however, had two run-in subjects that were unblinded, assigned to active treatment, which gave an opportunity to ensure the quality control and the smooth process of the protocol. Those two subjects per side are included in the safety analysis only, not in the efficacy considerations. And blinding was eventually confirmed with questionnaires to

the raters, the investigators, the caregivers and the patients.

This gives you an overview of the sites. I just want to highlight the fact that the principal investigators at each one of the sites are very experienced clinical trialists and have expertise in Alzheimer's disease and in the field of trials for Alzheimer's dementia research.

The inclusion criteria, as I mentioned, focused on patients with mild to moderate Alzheimer's disease, defined by DSM-IV criteria, and on the basis of the assessment by those experienced clinical trialists, MMSE of 18 to 26, and an ADAS-Cog above 17. Since the subjects underwent an MRI, as I mentioned, for the neuronavigation, the MRI was also used to rule out pathologies, for example vascular disease, that may raise questions or put doubt into the etiology of the dementia of the patients.

The patients could be on medications. And, in fact, the majority of them, over 80% were. The requirement was that they had to be stable on those medications for at least 2 months and had to continue on the same dose for the duration of the study.

The exclusion criteria were mostly around the issues that could potentially increase the risk for MRI or TMS.

And the primary efficacy endpoint of the study was the ADAS-Cog at 7 weeks. And then secondary efficacy endpoints included the ADAS-Cog at 12 weeks and the CGIC at 7 and 12 weeks. Of course, a big emphasis included capturing any adverse events, to assess the safety of the device and the intervention.

What I would like to do now is to pass it on Dr. Sabbagh, who will start to review the results of the study.

DR. SABBAGH: Thank you, Dr. Pascual-Leone.

I am Marwan Noel Sabbagh. I am the Director of the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada. I hold the endowed chair of the Camille and

Larry Ruvo Chair for Brain Health and professor of neurology.

I did serve as the site PI for the pivotal study. I am an advisor to Neuronix. I hold no proprietary, financial, or equity interest in the company or the investigational product. I am paid and reimbursed for my time and effort today.

I'm going to walk you through the data. First thing I want to talk about is the subject disposition. And we're going to walk through this from left to right. And the left-hand side, you see that we have 130 that were ultimately enrolled into this study. Twenty of these were run-in subjects, so each site was allowed to have two essentially open-label practice subjects so that they could learn, master, and familiarize themselves with the technology and the technique. These 20 run-in subjects were not included in the efficacy analysis. They were included in the safety analysis. One subject withdrew prior to initiating the study. Therefore, the safety population was 129 subjects, and ultimately without the run-in subjects, 109 ultimately went on to be randomized. That is 59 in the active group and 50 in the sham group.

In the primary efficacy population, that is the majority, 106 of the 109, there were 57 active and 49 subjects total; 106, of these 101 were observed during the first follow-up at 7 weeks, that's 95% of the sample, and then only 3 more subjects missed the 12-week, resulting in 98 subjects completing both study endpoints.

We also note here that the definition of per protocol population, of a subset of the primary efficacy population with no major protocol violations, with 98 out of the 106 in the primary efficacy population. In essence, the primary efficacy population is the ITT group. That means that they had been randomized and had at least one assessment and one treatment. Essentially, the per protocol group is the completers analysis, which means that they completed the majority of their visits and were included in that sample.

So for the people in this group, and I know that many of you are trialists, is that this

is a laborious study, heavy in its burden. Subjects were required to come in 1 hour a day, 5 days a week, for 6 weeks, and then had an observation period for another 6 weeks. Despite the laboriousness of the study, 30 treatment sessions, 90% of the subjects attended 90% of the sessions, and 90% of the randomized subjects attend the final follow-up visit. That is an amazingly good adherence rate to a trial of this scale.

I want to mention to you the balance and the rigor. Here we see the study demographics for the safety population. So this is the end of 129. If the Panel is interested, we can show similar charts for the primary efficacy population. This sample included roughly 54% men, 46% women. The proportion of men and women are equally balanced in both arms of the study. The mean age is approximately 77 years of age, again, balanced in both arms of the study.

As you can see, the active and sham groups were well balanced and matched on baseline, ADAS-Cog and Mini-Mental State Exam. And you see the ADAS-Cog is mild at roughly 24 points.

This is an important slide. I want to point out that this Committee has to understand that anything we're evaluating today, as you render a decision or recommendation, this is above and beyond standard of care. Eighty percent of the sample was on stable Alzheimer's medications, similarly distributed in both arms during the entire study. That is a metric or a measure that not a single drug or device has met in the last 16 years, that they have showed any efficacy above and beyond the standard of care. So this is a high threshold or high burden to meet.

I want to next comment on the safety data. As Dr. Pascual-Leone commented, there is substantial evidence for the safety of TMS for a variety of indications. Consistent with this experience with TMS therapy, the safety results for the pivotal study were very favorable. On this graph, you can see a breakdown of the adverse events by relation to

study. You can see only 15 events were deemed likely or definitely to be related to the device or the study.

From the subject's perspective, only 11 subjects or 14% of the sample experienced any related event. A related event was deemed as possible, probable, or definitely related. Related events were mild and transient, and now we will move on to break down these events.

As you can see, as has been reported, the events were headache, muscle twitching, skin sensitization, fatigue, and neck pain. They were mild in nature, most of them resolving spontaneously within a few hours. There were no withdrawal from study-related, device-related adverse events, what we would call a TEAE, treatment-emergent adverse event.

More importantly, on the serious adverse event, there were four unrelated SAEs reported in randomized subjects. There were no related SAEs in either group during the study. And I want to tell you that Dr. Pascual-Leone commented that there was a risk of seizure with TMS. As can be seen, there were no seizure events reported, either related or unrelated.

Of the four SAEs reported occurring during treatment but -- were reported but none during a treatment session or immediately following. Two unrelated SAEs occurred in the active group, one case of asthenia, which resolved in less than a week, one case of unrelated death. The subject was found deceased after complaining of GI symptoms. It was considered by the site PI and the DSMB to be considered unrelated to the study or the investigational product.

I would like to point out that the site PI for that, Dr. Agronin, is here with us today and can answer questions to you about this participant. It is clear, therefore, that this technology, this treatment is very safe, and there are no recorded adverse events of major CNS events.

Now I would like to report the U.S. pivotal results for efficacy. Before proceeding through the data, though, I would want to point out that all data presented will be observed data only, as you have seen in both our panel briefing material and the FDA's, without any imputations. If you would like to learn more on the rationale, our statistician, Dr. Lavin will comment. He is here with us today and can answer any questions on this matter for you later.

Moving forward, purple is active, sham is green. As you can see, in our background package, that as previously noted, the study did not meet its prespecified primary endpoint at 7 weeks. At 12 weeks the active group outperformed the sham group on ADAS-Cog and also on CGIC, reaching a statistically significant on chi-square of p-value of 0.037.

Furthermore, at 12 weeks, when considering responders on CGIC, only 16% of active subjects progressed or deteriorated, compared to 42% of sham subjects, with a p-value of 0.01 on the Fisher's exact test.

As we observe direct evidence of benefit, we wanted to investigate who benefited the most so that we can identify the participants that will be potentially eligible in the label per the analysis plan.

I want to comment to this audience, the CGIC is a blinded -- the rater who did the CGIC was blinded to the psychometric data, the randomization, the treatment assignment. And this is an interview, a semi-structured interview. For the people who don't know what this is, you interview the informant and interview the participant in a semi-structured interview, and you do that at each prescribed time point, and you use the same interview at the follow-up time points to baseline, and determine, compared to the baseline, if they're unchanged, mildly moderately better, mildly moderately worse. So moving toward 1 means you're getting better, moving towards 7 means you're getting worse.

Now we want to identify, who is the indicated population? What would the label

look like? Should this Panel approve this technology? As part of the primary analysis, baseline ADAS-Cog was prospectively included as a covariate to be evaluated. Also important, it was the only parameter to be tested in this covariate analysis, in the primary analysis. Inclusion of baseline ADAS-Cog as a covariate was based on the scientific literature, which indicates that Alzheimer's disease progression is influenced by a patient's ADAS-Cog score.

The analysis found a statistically significant interaction between baseline ADAS-Cog and study group at both 7 weeks, with a p-value of 0.029, and at 12 weeks with a p-value of 0.01, resulting in a non-homogenous effect across different baseline values. In essence, we're showing that milder subjects showed better outcomes. And it is not unusual, and I'll say this again moving forward, it is not unusual to select particular groups that are likely to benefit. That's just common practice in the clinical space, in clinical research space in Alzheimer's disease.

So in light of the analysis that I just mentioned, a literature review was conducted, and based on this review, it was estimated that subjects with baseline ADAS less than or equal to 30 were in the milder stage of the disease and progress at a different rate. A threshold of 30 was selected based on the literature, including two examples. Ito did a meta-analysis of 52 studies including 20,000 participants and found that the subjects with a baseline greater than 30 deteriorate faster than subjects with a ADAS less than 30 or equal to 30.

Similarly, the Stern examined the 1-year change rate on ADAS-Cog among various states of disease severity and concluded that subjects with baseline equal to 30 deteriorate 50% faster than subjects with baseline ADAS equal to 20, and other studies show similar trends. It is therefore evidence that the baseline ADAS greater than 30, which would essentially be saying moderate Alzheimer's dementia, not only presents a more severe state

of the disease but tends to progress more rapidly than subjects with a baseline less than or equal to 30.

In addition to the natural history studies, that threshold of 30 was also confirmed by TMS cognitive training studies. Rutherford performed a small study that investigated combined TMS with cognitive training intervention and specifically identified a threshold of 30. Lee, in Korea, performed an independent study using the neuroAD system and concluded that mild patients with a baseline less than or equal to 30 respond better. Consequently, in her next study, Lee limited her included population accordingly. You will hear more about the outcome of those studies later in our presentation in the supportive information section.

Zhao, in China, performed a similar study without any connection to Neuronix or the neuroAD technology and concluded the same results. I want to point out that all of these studies support using an upper threshold of ADAS equal to 30. Note, however, that all studies that I just mentioned were published after the U.S. pivotal study started, so their conclusions were not known and did not influence the decision-making process when it comes to this study.

I think we all agree, it is not surprising that in our field of AD research that subjects respond different depending on what stage of disease there are. And subjects in the milder stage of the disease tend to respond better, in this particular case, to the intervention.

Our data supports what the literature just showed. In addition to the prespecified covariate analysis and the literature review, a cutoff of baseline ADAS equal to 30 is supported by our findings in our own study. What I'm trying to do is give you what the indicated population would be, which would show that both cognitive training component and TMS component differ in subjects with baseline scores of less than or equal to 30.

So you see on the graph is that the higher the ADAS, the lower the motor threshold,

the lower the ADAS, the higher the threshold. There is a significant correlation between the motor threshold and the ADAS score, with a correlation coefficient of -0.4. Subjects with lower ADAS-Cog scores less than or equal to 30 had higher motor thresholds and higher TMS power, which is statistically significant at a p-value of 0.028. Therefore, they can get more stimulation, which helps their brain function more, and it's directly correlated.

Now we come to the cognitive training component of the intervention. On the cognitive training component, the subjects with baseline ADAS-Cog ≤ 30 advanced or improved significantly as they progressed through the technology, through the training, at p-value of 0.01, implying that subjects benefit more from the cognitive training in milder stages and was probably too challenging for subjects who were in the moderate stage, meaning ADAS greater than 30. Thus the combination of the prespecified and additional analysis as well as the literature described led to an identification of a clinically meaningful subgroup of subjects with a baseline less than or equal to 30.

As we all know, differentials in treatment outcomes based on disease severity is not uncommon in Alzheimer's therapies. And we would also want to mention that the group of subjects in the indicated population now that I've already articulated will end up being ADAS less than or equal to 30, represents 85% of the sample, so we're not just throwing out a big chunk of the sample. It still represents the overwhelming majority of the sample.

And I want to point out that had we cut off anything below 30, the results would have been comparable, and so that's how we come to the indicated population, should this Panel approve this technology, would be for mild to moderate Alzheimer's dementia with a baseline ADAS-Cog ≤ 30.

Here I show you the primary data in the indicated population again, baseline ADAS-Cog ≤ 30. The figure shows baseline 7 and 12 week in the indicated population. As you can see, as would be expected, both groups improve in the first follow-up without any

significant difference. As you would also expect, at 12 weeks, the sham group goes back to normal, as the placebo effects tends to wear off, and the active group continues to improve with a delta of -2.11 points. The between-group difference at that point reaches -1.6 points in the primary efficacy population, nearing statistical significance, and -1.79 in the per protocol population, favoring the active group reaching statistical significance at a p-value of 0.049. Dr. Pascual-Leone will further discuss the timing of response to the treatment.

This slide, I want to spend a few minutes talking about the S-curve in the indicated population, as it is a common presentation format to show Alzheimer's disease therapies using an S-curve. The red line is the zero value in the middle of the chart, so anything left of the red line is improvement. So you want to move in a negative direction. Anything right of the red line is declining.

I want to point out, in the left-hand panel, you see no difference between sham and active treatments; however, in the right-hand panel you start to see that active is favored over sham at multiple time points -- I mean at multiple cut values. And 12-week distribution shows greater efficacy with over 2/3 of the subjects showing some improvement and 1/3 of the subjects showing significant improvement, meaning an ADAS delta of 3 or 4 points. And that's a pretty robust effect in 12 weeks, is 3 or 4 points. That would be the black and blue lines you see on the right-hand panel of the graph, again showing that the majority of patients did improve in the treatment compared to sham and a significant plurality had a robust improvement.

This graph shows the CGIC in the indicated population for both the primary efficacy and the per protocol populations at both 7 weeks and 12 weeks. On the CGIC, very little difference was seen between groups at week 7, slightly favoring active subjects. At week 12, the between group differences favors the active group and reaches statistical significance on chi-square with a delta of 0.40 between the groups in the primary efficacy

population and 0.45 in the per protocol population.

I know I mentioned it before; I'll mention it again. The blinded clinician who did the CGIC, the clinician's global impression of change, was unaware of the treatment assignment, was unaware of the ADAS data. And the blinded clinician could even identify there was an improvement after 12 weeks, significantly so in the active group compared to the sham group.

Also indicated in the primary efficacy population, only 12% of the active subjects deteriorated while 40% of the sham subjects deteriorated. This is a significant difference with a Fisher exact test p-value of 0.01.

To further demonstrate the favorable performance of the active group compared to the sham group in the indicated population at 12 weeks, we assessed change in ADAS-Cog and CGIC on the dual and responder endpoints. This is a historical way of looking at Alzheimer drug outcomes for drugs. I want to point out to this Panel, this is a very high threshold to meet. No other drug or device has met that threshold in the last 16 years. In fact, there has been multiple statements around whether this might change over time, but at this point and at the time of the design of the study, this still remains the standard to be met.

The left bars show the percent of subjects with improvement or no deterioration on both scales. The right bars show the percentage of subjects deteriorating on both scales. Importantly, 64% of active subjects improved or had no change on both assessments compared to 43% of sham subjects. In addition, only 7% of active subjects deteriorated on both measures compared to 23% of sham subjects.

Thus, neuroAD significantly outperformed the sham group in the even hard-to-meet dual endpoint analysis. And I will point again, this is above and beyond standard of care. This is a threshold that has not been met for the last 16 years, that this is treatment plus

background medication, which then strongly favors active over sham treatment.

And, in summary, when you're deliberating, considering this, the first thing you have to consider is: (1) this is a very safe technology, with an amazingly good, high adherence rate; (2) the indicated population has been identified, mild Alzheimer dementia, is based on a relationship between the baseline ADAS-Cog and the outcome; (3) the benefit is additive; 80% of the entire sample was on stable AD medications throughout the study, again, a high threshold to meet; (4) the 12-week efficacy data in the indicated population shows a -1.61 difference, which is clinically meaningful, favoring active over sham, and 40% of active subjects showed at least 3 point improvement, and more than 70% showed some improvement at 12 weeks compared to baseline.

The CGIC endpoint, again, blinded clinician could identify that there was -0.40 points, clinically meaningful in active outperforming sham. In the indicated population, the very difficult-to-meet dual endpoint of ADAS-Cog and CGIC shows that 64% of active subjects improved or showed no change on both measures compared to 43% of sham subjects and that only 7% of active subjects deteriorated on both measures compared to 23% of sham subjects.

The conclusion is, as Dr. Alpert articulated in her opening statements, when we look at the de novo standard, the safety has been met, the efficacy has been met, and safety and efficacy is established for the indicated population.

And with that, I will now turn over to Dr. Pascual-Leone to discuss additional supportive studies. Thank you.

DR. PASCUAL-LEONE: Thank you very much, Dr. Sabbagh.

So as I mentioned before, and as you heard, there is not just the U.S. pivotal study but a number of other studies. I'd like to briefly review two studies in Korea, the pilot and the pivotal studies, because they were done independent of the company with the same

protocol.

This chart shows you the time course of them. I think what is important to note is that the pivotal study, which focused on patients with an ADAS-Cog at baseline of less than 30 because of the results of their own pilot study, was started before the results of the pivotal study were available.

The demographic of the Korean studies and the U.S. pivotal studies are shown here. They are a match for most of the parameters. I think what is noteworthy is that, consistent with other TMS studies, the motor thresholds in the Korean studies were higher than those in the U.S. pivotal study, implying that the patients could receive higher absolute intensity of TMS, which may have contributed to changing the time course of the response.

The results of the studies show consistent findings in terms of safety as well as in terms of efficacy at 12 weeks, as you see here. But at 7 weeks, there is a clear difference in the mean ADAS-Cog efficacy metric between the two Korean studies showing benefit and the U.S. pivotal study not showing any benefit at 7 weeks, as you heard, and thus missing the endpoint that was prespecified.

As mentioned, the TMS higher intensity may have contributed to this, but in addition to that, if one looks at the results at 7 weeks, what is apparent in the comparison of the three studies is the large overlap of the confidence intervals, as you see here. So the separation of the means is there, but the confidence intervals are very broadly and largely overlapping.

In addition to that, obviously, also in the pivotal study, even though the mean is shown above, one can find individual patients, as shown here, with three such examples, that respond faster in terms of the time course and that have therefore a greater effect at 7 weeks than at 12 weeks. It is not surprising that the time to achieve maximum benefit would vary across patients.

Now, the FDA has appropriately raised questions about why the effect of the neuroAD may increase after the end of treatment or be greater at 12 weeks than at 7 weeks, and it was mentioned, it is not surprising that there would be variability in the response to reach maximal benefit across patients. There are mechanistic considerations to be made. Although not fully defined, it could reflect the time required for the consolidation of the effect and be dependent on the intensity of the stimulation, hence making differences between different studies, particularly smaller ones in Korea.

But, in addition, such delayed quote/unquote "effects," apparently later coming effects developing over time, have been shown in TMS or found with TMS in a variety of other indications, including nonfluent aphasia, cognitive benefits in autism, OCD results, or even in depression.

If one looks at 12 weeks, across this U.S. and Korean studies, what one sees actually is a much greater robustness and consistency of the results, which in a meta-analysis show to be significant with an overall effect of -1.66 in the ADAS-Cog and without the confidence interval of that meta-analysis crossing the zero point.

Now, as we talked about earlier, there is, in addition to the two Korean studies, a number of other studies, both clinical trials as well as clinical experience. And when one looks at all of those, as shown here in the forest plots, my point here is simply to show that despite the differences across studies, they consistently, all of them show a beneficial effect, with all the points across all the studies being to the left of the zero line.

Now, the FDA has raised a number of questions that are important and that I would like to take a few minutes to go through. We've tried to address them with Dr. Sabbagh showing you some of the data. The first one is whether the ADAS-Cog of less than 30 is a clinically valid subset, and thus the supplemental data, including these additional studies adequately support the subgroup. As Dr. Sabbagh shared with you, this was not a picking a

number that would explain the results or would come up with the positive results, but rather was based on both the literature review that he summarized, a mechanistic argument for both the TMS effects and intensity as well as the cognitive training, whether the patients would be able to engage or not in them.

And ultimately, as I just briefly shared, the Korean studies we believe provide further experimental validation, since those investigators, independent from Neuronix, after completing the pilot study and reaching the same results as the U.S. pivotal study, decided a priori, prospectively, and independent of the pivotal study in the U.S. to select patients with a ADAS-Cog of less than 30 for their pivotal study.

Can the ADAS-Cog be used to select patients is the second question that appropriately the FDA raises. And the ADAS-Cog is indeed a research tool, not a clinical tool per se. The experimental evidence from the Korean pivotal study shows that at least, not surprisingly in the setting of clinical trials, it can be used for that, with trained individuals. But as you heard from Dr. Baror, in Australia, the Australia FDA equivalent approved the neuroAD with an ADAS-Cog of less than 30 as a criterion, and in clinical practice, that is being implemented and used successfully there, and you will have the opportunity to hear about that in the Open Session further.

The company has developed a training program and is committed to continue to train individuals in clinics if this is approved.

A very important question that the FDA raised, and that I touched on in the contrast between the Korean and the U.S. pivotal studies, how should the 7-week versus 12-week results be viewed, this apparent later-on effect. And as I mentioned, the first thing to focus on is that a careful assessment of the results across the various studies where it shows is broadly overlapping confidence intervals at 7 weeks and a much more consistent and robust effect at 12 weeks, so that an argument can be made that what we're seeing is the

reflection of two processes, one a mechanistic consideration where the TMS combination with the cognitive training takes time to fully develop its effect, and therefore the time course until they reach that point varies across individuals, and with that, would vary across studies. But that is arguably a hypothesis, and there is some data to the time course, and to the modulation of plasticity from separate studies, including some of my own center in Harvard that I can offer and share in the discussion session if there is interest.

But on the other hand, the question from the FDA as to whether the benefit outweighs the risk, I think can be fairly straightforwardly answered. As we shared, there is over 400 subjects across the studies. Consistently across all the studies, including the U.S. pivotal study, the neuroAD has been shown to be safe. And consistently, across all the studies, they all find a beneficial effect that is particularly obvious for some patients. Nearly 50% of patients, in fact, across the studies show 3 or more points of improvement on the ADAS-Cog. So there is a subset of patients with a clear benefit that can be identified so that if you consider the safety versus benefit weighing, I think that the evidence provides support for the benefit outweighing the risk overall.

Now, the FDA has asked two additional questions: Is the benefit clinically meaningful, and questions around the use of ADAS-Cog and CGIC in this context. And to address those questions, I'd like to introduce Dr. Schneider, who will address them.

DR. SCHNEIDER: Okay. Thank you, Dr. Pascual-Leone.

Good morning. As I was introduced, I am a Professor of Psychiatry, Neurology, and Gerontology at the University of Southern California. USC has made it to the front pages of the *New York Times* and *Washington Post* rather regularly this week, and I hope you won't hold that against me.

I'm serving as a consultant for Neuronix, and I'm paid for my time, travel. I don't own equity. I have no interest in the outcome of the meeting. But last year, I was asked by

Neuronix to respond to some questions that the FDA Devices group had about the CGIC and the ADAS-Cog, and I wrote a detailed letter to Dr. Pena about that.

My background, I think, is probably important to know a bit, that my academic background has been actually rather extensively in the CGICs, the ADAS-Cog, and the clinical trials methodology in general. Our group and my colleagues have funded grants and clinical trial simulations that attempt to assess better methods, or better methods for Alzheimer trials. My comments largely, though, and my expertise is in drug development and not in devices.

As part of my work, I'm also funded with a group of colleagues to look at practice effects and novel outcomes, to try to develop novel outcomes for prevention trials. And then, most importantly, from the beginning of the development of Alzheimer's disease clinical trials in the very late '80s and '90s, I led a committee of the UCSD Alzheimer's Disease Cooperative Study that attempted to approach FDA's guidance on global scales by developing the ADCS-CGIC. The ADCS-CGIC is one example and the most commonly used example of a CIBIC, a clinician's interview-based impression of change, with caregiver input.

At about the same time, I had consulted with Parke-Davis in the development of tacrine. And the Parke-Davis Warner-Lambert Pharmaceuticals was working with FDA and other academics and developed also a similar CIBIC that was used in the early studies with tacrine. Dr. David Knopman led the development of that. And I wanted to give you that background because that's my perspective in the comments that I'll make.

And I'm sorry it was a bit lengthy, but I was asked to respond and wanted to respond to FDA's question number 2, the minimum amount of improvement on the ADAS-Cog, and what is the minimum amount of clinically meaningful improvement on the CGIC. I think it's probably important, in the interpretation of this study and of other studies, and at least I welcome the chance to share my perspective here.

And now, since 1989, 1989's FDA-sponsored symposium, in 1992 an advisory committee that dealt with methods and outcomes in Alzheimer's disease, and then overlapping a couple of advisory committees on tacrine, it's been fairly clear to me at least that from mild to moderate Alzheimer's dementia studies, what constitutes clinical meaning is a combination of outcomes where one is able to see a cognitive effect on a cognitive battery and that that is supported by a global or functional outcome.

So, de facto, the formula for a dual outcome in mild to moderate AD is significance on an ADAS-Cog plus a CGIC, or an ADAS-Cog plus a functional rating. You know, it never had to be the ADAS-Cog, but that's actually what it's turned out to be. Overwhelmingly, the ADAS-Cog has been used as the index of cognitive outcomes. It's been much criticized when it fails to show efficacy. Critics will say, well, it wasn't sensitive enough. There are practice effects. There are learning effects. It's a dirty measure. When there is efficacy, the opposite is, oh, well, it was accidental. Studies were too small. Perhaps it wasn't administered correctly. But, basically, the ADAS-Cog is a perfectly reasonable cognitive composite within the range of mild to moderate AD.

So by overview, with the market, and by comparison with the marketed cholinesterase inhibitor trials, a mean outcome on the ADAS-Cog is about one -- drug-placebo difference is about 1.49 to 2.37 points. What I want to emphasize is there's no minimum mean drug-placebo difference that automatically confers clinical significance. And, similarly, in within group comparisons, there's no particular minimal mean change over time that automatically means this is a clinically meaningful change. The importance of this change relies on the convergence and of other measures, such as a global, such as a functional rating which helps to support it.

So as early as 1991, a division director of neuropsychopharm products at the FDA said that if an experienced and unbiased clinician can detect a global change based on an

interview, then that change can be assumed to be clinically relevant. That is within the context of supporting other outcomes. And that supported the developments of the CIBI and the CIBIC+ variations.

Okay. I just want to point these out before I close. This is just the visual representation of meta-analysis averages from marketed cholinesterase inhibitors of the drug-placebo differences in 12-week and 26-week studies, showing the mean differences that I mentioned. And then if you look at the middle blue, the middle purple column on the right, the -1.16 represents the TMS cognitive training system versus sham difference on the ADAS-Cog, about 1.61. The point here is that overall the effect is in the same range as cholinesterase inhibitors.

Then moving to, just again by example, to the ADCS-CGIC, the ADCS-CGIC was used in the donepezil pivotal trials, and a version of a CGIC was used in the rivastigmine trials. And what you see is that the mean effect of this ordinal scale, when the ordinal scale is averaged, is about 0.36, 0.39 for donepezil, and by comparison with the TMS cognitive training system versus sham, the difference is about 0.40. My point here only is that the outcomes as presented earlier are in line and consistent with marketed drugs.

And then to address the idea of why -- it's hard to say that there is a particular minimum difference that is between drug and placebo in this case that is by definition clinically significant. I just want to show these cumulative distributions of change scores here on the ADAS-Cog. On the right-hand side is from the prescribing information for Aricept and donepezil from a 12-week study. And the point of this is to show that whether you take a cut of 2 points is significant, 3-point difference, or 4 points, or 7 points, wherever you drop that vertical line, you see a consistency where the drug treatment, where a greater proportion of patients on the drug treatment are doing better than patients on placebo. And, overall, this was statistically significant. So setting this kind of cutting score

can be arbitrary.

The other part to this with an ADAS-Cog is that the ADAS-Cog is not an interval scale. And a 3-point change in patients who are starting out with 15 or 18 deficit points, relatively mild dementia, means a lot more than a 3-point change in patients with moderate dementia, let's say starting out with 40 points, 35 points of deficit. There the improvement is 40 to 37, 35 to -- what's changing there is probably not important and is different. So, again, taking the average can be difficult.

I wanted to show the same kind of distribution here with the ADCS-CGIC. The right hand is the distribution of CIBIC+ changes with donepezil in the 12-week study, showing in general that amongst those who are improved, there are more patients taking drug than placebo amongst patients who were judged by the clinician to be worse, minimally or more moderately worse. There were more patients on placebo than on donepezil.

Overall, this was significant. Overall, it also conveyed that an absolute number of patients benefited from the drug intervention compared to placebo. On the left side, I think you saw this earlier. This is a similar distribution of CIBIC+ scores in the indicated population group of the TMS cognitive training system.

So, just in summary, the ADAS-Cog is a composite neuropsychological scale. It's imperfect, but really it's about as good as other cognitive scales for this purpose in this area of drug development and is used to demonstrate overall cognitive benefits. The ADCS-CGIC is one example of a global that can be used to indicate clinical meaning. When they converge, I think there's a reasonable assumption that what is happening within this clinical trial is clinically significant to individual patients.

And I just want to thank you for listening to this, and to this overview. Again, I mention there's a letter that detailed this to greater degrees. And thank you for the invitation to participate.

And I need to now introduce or reintroduce Dr. Sabbagh and Dr. Pascual-Leone to sum up the presentation.

DR. SABBAGH: Your charge is important. Your decision is consequential. I know you probably heard this morning there was negative results reported by another sponsor for another program, at least a failed interim analysis. That probably sets back the field probably 3 years. And so what you decide today or deliberate upon today actually matters not just in this room but to thousands of people.

I have been PI, site PI of over 100 studies, and global PI for seven or eight. Based on my experience, it is logical to see an effect at 12 weeks, and in none of the studies that I have done would I have expected to see an effect at 7 weeks. As a researcher, I would not expect to see an effect so early, so I think that the 12-week is more meaningful. I also note that if we adopt the NCID standard of 3 to 5 points improvement, then amazingly, the drugs that we have approved, many of them would not have made that, have met that threshold.

I want to also tell you that, kind of summarizing where we're at, this is an unmet clinical need, and there is need for effective, additional effective treatments. I think we've put to bed the idea that neuroAD is a safe technology. The safety has been demonstrated with clear low risk. The efficacy has been demonstrated when we identified the indicated population of mild Alzheimer's dementia. We show clear, meaningful benefit on the ADAS-Cog and the CGIC, and the difficult-to-achieve dual endpoint, that the indicated population is confirmed over multiple independent studies, that this benefit is demonstrated above and beyond the standard of care medications and not compared to placebo alone, that the 12-week threshold is a more clinical meaningful benefit, more clinically meaningful relevant time point.

I want to make a few more points. As you will hear later today, I recently recommended to one of my patients to make the effort to travel to Israel to undergo this

treatment. You will hear from their experience. But I would emphasize to you that had I not strongly believed in this technology, I would not have recommended this for my patients. Of course, not all U.S. patients can go overseas to get this kind of technology. That's why we need to have this treatment available to here. The totality of the evidence supports that there's a clinical meaningful benefit that outweighs the minimal risk.

I want to say one thing. Tonight I'll get on the plane, and I'll go back to Las Vegas, and I have clinic tomorrow, and I see patients tomorrow. And every one of them is dealing with a scary, degenerative brain disease. And I am dealing with their diagnosis. I'm dealing with their management. I'm dealing with trying to give them an answer, a future, hope.

People think we're shooting for the cure. We're shooting for incremental progress. This is incremental progress. You can break down the methodology, you can break down the statistical analytical plan, but at the end of the day, this is about patients. And so you have an important decision to make in front of you, and I want you to consider that as you deliberate later today.

Thank you.

DR. PASCUAL-LEONE: Thank you, Dr. Sabbagh, and second, I'm Alvaro Pascual-Leone.

And I talked at the beginning about the neuroAD addressing an urgent need. We've echoed that a number of times throughout the presentation. It offers a multi-modal therapy option. And I laid out some criteria of what adjunctive therapy should fulfill, and hopefully we've shown you that that is indeed the case.

In regards to the safety, it is a safe intervention. In regards to the measurable effect, for the right patient, it has a clear benefit. In fact, it delivers what might be described as a dramatic benefit of 3 or more points in the ADAS-Cog for over a third of the patients. It has some benefit for an additional third of the population on top of the standard of care.

This is derived from over or nearly 400 patients across different studies. But there is no question that neuroAD is not a curative treatment, is not a disease-modifying treatment for Alzheimer's disease. What I believe it is, is a safe intervention. And it is, for the right patient, effective to minimize their cognitive disability. It is additive to the standard approved medication regimen, and it offers an opportunity to improve, to gain time, to participate more meaningfully in activities of daily living, with very little down side in terms of risk. And that evidence comes not only from the pivotal study but is supported and confirmed by 13 additional studies.

Given that, I believe that, at this point, one more study would not fundamentally change those conclusions. And so it would effectively only delay, potentially by several years, the potential benefit to the right patient and the access to the technique to U.S. patients and their families.

I see patients as well, just like Dr. Sabbagh, and I cringe by the scenario of having to recommend to them to go elsewhere, to go to Europe or to go to Australia. That has significant not just financial burden but significant impact on the disease for these patients, to spend nearly 2 months at a unfriendly or at least unknown place. It's a burden to the patients. And I don't think that we should be putting patients in that predicament of having to make that decision.

So I think that we have the opportunity to continue to learn about this technology. There is much to still learn. There is no question about it, to continue to learn about the intervention, to continue to improve the protocols, but to do so while helping the right patients have access to the interventions that patients in Europe, in Australia, in Israel already have access to, if supported by their clinicians.

In that decision, the balance between risk and benefit is important, but it's important in framing it as the de novo indication, I understand frames it, which is the

likelihood of probable risk against the likelihood of probable beneficial outcome. And I believe that we owe it to the USA patients that we see to have access to that therapy today, rather than years from now, and that more learning can happen while we continue to help the patients.

Thank you very much.

DR. JENSEN: Thank you. Are you done?

MR. BAROR: So, yeah. Just final notes, if it's okay.

So thank you Dr. Sabbagh, thank you, Dr. Pascual-Leone, and obviously thank you, Dr. Schneider and Dr. Alpert.

Before I hand over to the Panel, on the company's perspective, Neuronix has developed over the last 10 years for the development of the system, and we are committed to ongoing research in the postmarketing setting. We are further committed to continue to provide appropriate training and customer support, as we have done until now out of the U.S., where device is already in commercial use.

And, finally, wish to thank the FDA and the Panel members for giving us the opportunity to speak and present our data in front of you. And special, I think, thank you for the patients and caregivers for being with us for all these years.

Thank you.

DR. JENSEN: I'd like to thank the Sponsor's representatives for their presentation. Does anybody on the Panel have a brief clarifying question for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during the Panel deliberation session. So anybody?

Oh, we've got hands up. Okay, so let's start at this end, over here. So that would be Dr. Rosenberg.

DR. ROSENBERG: What about specific cognitive domains? As long as we're doing

post hoc analyses, one wonders if you could deconstruct the ADAS-Cog. At least you can look at memory and attention. It really isn't designed for that, but once again, as long as you're doing these post hoc analyses, might be able to show a better effect.

DR. SCHNEIDER: So, Lon Schneider. I'm going to take a part of this question.

So the ADAS-Cog was designed as a composite. The way it was created was to go through patients in the Bronx VA with various subtests, neurocognitive subtests, to see which ones mild to moderate dementia patients could perform at roughly in the middle. Then it's a sparse rating, a sparse rating of memory, orientation, language, etc., and it's put together as one composite rating.

When we start to deconstruct it, you're left with really very, very small numbers of questionable validity. So I'll let the statistician deal with this study.

DR. JENSEN: So, Dr. Proschan?

DR. PROSCHAN: Yeah. I wondered why you had a sham cognitive therapy. I mean to me, it makes sense to have, you know, the sham, you know, transmitter but use the same cognitive therapy for both arms.

MR. BAROR: Dr. Pascual-Leone?

DR. PASCUAL-LEONE: Thank you for that question. I share the interest in that question, and in fact, I think it's an important one. And so prior to the U.S. pivotal study, we had done as a trial, at Harvard, that I'll share the results with you in a second. But before doing that, let me clarify, as I think it's important to think of the intervention not as TMS and cognitive training, as two different domains, but the -- or interventions, but really as an integrated, single intervention.

And the reason for that is because it is designed exactly that way, as a short burst of stimulation coupled with specific tasks. And that doesn't invalidate the interest in the question of could the cognitive training alone have the effect, which is what you're asking.

And we asked that, too, in a study.

And if I can have the slide in position number 1.

The study involved a small, three-arm trial -- the position 1.

And so patients were randomized to either real-real, as you heard, real TMS and real cognitive training, with the neuroAD system, sham-sham, so sham intervention for cognition and for TMS, or real cognitive training with just the sham TMS. And the sham TMS was important to mimic the perception by the subject, the disruption and so forth.

It was a 6-week, five sessions per week, same design. It's a small study. But the point was that what we saw was basically a benefit only in the real-real. And that is consistent with a number of different additional measures. The amount of cognitive improvement on the tasks during the 6 weeks of training was flatter in the sham TMS-real cognitive training than in the real TMS-real cognitive training, consistent with the notion that what the TMS is doing is priming a circuit and making it possible for the subjects to benefit more and therefore have a, quote, "enhanced learning," or benefit from the cognitive training during the sessions, consistent with that steepness of the learning curve during the 6 weeks, was correlated, that was correlated with the ultimate ADAS-Cog.

So I think that what is going on is that that integration enables more benefit to be drawn from cognitive training. If cognitive training alone is useful in Alzheimer's disease, as you all independently well know, is an unclear issue and a debated one. There has been a number of meta-analyses looking at this. There is no clear evidence in support of it at this point. And it may have something to do with the fact that patients with Alzheimer's disease, because of the toxicity of oligomeric free-floating amyloid on synaptic plasticity have abnormal mechanisms of plasticity and therefore derive insufficient benefit potentially from the cognitive training.

So I think the bottom line is that the cognitive training of the neuroAD alone was not

sufficient when coupled with sham stimulation to promote a benefit.

DR. JENSEN: Dr. Goodman.

DR. GOODMAN: I want to stay with the issue, questions about the cognitive training. Although you dismissed that, that you say that the cognitive training had no effect, it looks like the magnitude of effect is about similar to what you're showing in the current study. So why are you dismissing it?

DR. JENSEN: Put that slide back up, please.

DR. PASCUAL-LEONE: I'm not dismissing it. I wasn't aiming to dismiss it. What I was simply saying is that the effects I said we saw in the combined intervention were significantly greater than what we saw in the --

DR. GOODMAN: Got it.

DR. PASCUAL-LEONE: -- cognitive alone. And if you look at this in the cognitive alone compared to the no intervention with the sham-sham, there was no significant difference there.

DR. GOODMAN: I'm sorry. Could I ask a follow-up question along the same lines? Was there any way of evaluating performance on the cognitive training? In other words, was there some way of looking at, comparing the two groups with respect to how well they did and whether it be in errors or time to response?

DR. PASCUAL-LEONE: Yeah. Thank you for that question. That's what I meant with steepness of the learning curve. So we looked at each one of the cognitive tasks throughout the 6 weeks of training on the performance of the patients, both in terms of errors and in terms of response time as well as in terms of the advancement across the task. It was an adaptive design, so that if the subjects were performing better, the tasks were becoming progressively more difficult.

And basically what we found is that when coupled with the real TMS, when primed

by the real TMS, the learning curves were steeper. They were advancing faster through the sessions than when coupled with the sham TMS.

DR. JENSEN: Okay. So please stay there because there's -- five people have questions for you. I'm going to start first with Dr. Dorsey and then go to Dr. Knopman, and then we're going to go down this row. Okay?

DR. DORSEY: Three very short ones. One, you indicate the number of AEs was 63 versus 31. Could we get a table of the AEs in the pivotal trial? Second question is how many subgroup comparisons did you do after the study was completed? Third question, what corrections, if any, did you do for multiple statistical comparisons?

DR. PASCUAL-LEONE: I think I'm the wrong person for those answers, Dr. Jensen. I'm sorry.

MR. BAROR: Sorry. Can we do one question after the other? Then we know who to direct to.

DR. DORSEY: First, number of AEs was double in the pivotal study. Could we get a table identifying the 63 versus 31 AEs in the pivotal study?

MR. BAROR: The one that discuss it or the one that --

DR. DORSEY: Just a table.

MR. BAROR: We'll provide it offline. Is that okay?

DR. DORSEY: Just -- yeah, perfect. Second one, how many subgroups did you compare after the study was completed?

MR. BAROR: Okay. So this I will refer to Dr. Lavin.

DR. DORSEY: And then third, did you make any correction for multiple statistical comparisons?

MR. BAROR: So that's also for Dr. Lavin.

Dr. Lavin.

DR. LAVIN: Hi. My name's Phil Lavin. I'm a paid consultant to Neuronix. And my travel and my time here is being compensated by them. I have no equity interest in them, nor do I have any stake in the outcome.

Regarding the subgroup analyses that were done, I'd like to be open with you and straight. There were no subgroup analyses done that were post hoc. All of the subgroup analyses that were done were defined in the original protocol and the original SAP, where we looked at the -- and we had advance -- stated, back in, when the protocol was written, that there would be an interaction between the baseline ADAS-Cog and the treatment.

We subsequently did not do any subgroup analyses, fishing within age, fishing within the MT, or fishing within any of the other baseline covariates. We followed very closely the SAP. And in terms of the issues of multiplicity, they're certainly minimized when we're not really doing those extra subgroup analyses.

Now, in our -- in preparation for the meeting today, we did look at the performance, based on different cuts, for the baseline ADAS-Cog, but if you're interested, we can show those to you. It may be early to do that in the discussions, but we have them right here in the slide.

You can put that up.

And as you can see, the results are quite robust. Within the range of 20 to 30, that's the middle range, you see a -1.61 for our 30 cut, which is again defended by five publications in the literature, which were not known at the time that we wrote the original SAP or wrote the protocol. But we do want to take advantage of the events which occur and are published that support the 30 cutoff. If you changed it to 25, you'd see a -1.46. If you changed it to 20, you'd see a -1.64. So we're consistently in the zone. And staying at that point of less than or equal to 30 gives us a subgroup of 85%. So I would like to basically close my long-winded answer there.

DR. DORSEY: So I have the statistical analysis plan, dated February 23rd, 2016, from Neuronix. There's no mention of an ADAS-Cog cutoff analysis for less than or equal to 30.

DR. LAVIN: Yeah. Well, the cutoff emerged from the results and from looking at the literature, as you heard from the presentations. So our decision to go with the 30 cutoff was predicated by the compelling five publications that we cited earlier.

DR. DORSEY: So it was not prespecified in your statistical analysis plan?

DR. LAVIN: Well, what was prespecified in the --

DR. DORSEY: I just asked the question, yes or no?

DR. LAVIN: It was specified in the analysis plan that we would be looking at an interaction. That is in there, and as part of that interaction investigation, this is the way that you would execute it, by looking at specific thresholds, once you saw the significant p-value of 0.029.

DR. DORSEY: Were those thresholds prespecified, yes or no?

DR. LAVIN: Yes, they were.

DR. DORSEY: Can you show it to me? I don't have it here.

DR. JENSEN: Well, if the Sponsor has it available, we can look at it at a later point, but we need to move on to some other questions.

Dr. Knopman, then we're going to go down this row.

DR. KNOPMAN: I thank you for your presentation. I too am involved in taking care of people with dementia, and I have the same problem that I'm going to have to face tomorrow as well. However, I don't accept the premise that there was a benefit, but supposing hypothetically that there was, after 12 weeks of -- including only 5 weeks of therapy, what's your expectation of how this device would be used over the long term? You elided over the fact that most of the other studies in this field, all of the other studies since 1992 have been at least 6 months in duration if not 18 months or longer. How do you

propose, if there was a hypothetical benefit, of using it long term? You don't provide any evidence for that. This was a 6-week intervention.

MR. BAROR: Right. Thank you for the question.

Just before I hand over your question to Dr. Pascual-Leone, as for the question of Dr. Dorsey, I would like to correct for the record our answer. You are correct that an ADAS-Cog specifically of 30 was not prespecified in the statistical analysis plan.

DR. DORSEY: Thank you.

MR. BAROR: Dr. Pascual-Leone, please.

DR. PASCUAL-LEONE: Thank you very much for the question, Dr. Knopman.

I agree, in fact, to make your point more prominent, I worry that if we had an intervention that had a beneficial effect on patients that didn't have any sustainability, that they just had a little window of benefit without sustainability, that that would potentially be almost more cruel than to not have anything to offer them. So I think it's a very important issue.

As I was mentioning earlier, the decision was to focus on the acute effect, hence the duration of the effect, and then assess whether there was cognitive effect there. And so there was no longer general follow-up set up in the study itself. That was the conversation done with the FDA in terms of the design. However, we have a follow-up of those patients from their clinicians seeing them. It's more sort of anecdotal evidence than a study. And we have the experience in the clinical settings where the technique is being used.

And what we know from those instances is that the effect, consistent with what is known, for example, for TMS in depression, has a duration of time that in this case spans about 6 to 9 months, on average. A number of those studies have been published, in terms of the clinical evidence, with improvements in the same range acutely as the U.S. pivotal study, and with durations of benefit that range from 6 to, in one of the studies, 24 months.

DR. KNOPMAN: Doesn't that seem to be an important question to know now?

DR. PASCUAL-LEONE: Well, I -- sorry. I'm not sure if I'm supposed to answer, but I think it is a different question than whether or not the intervention has an acute effect. And given the focus of the indication, as you heard, the focus on the acute effect, that was the decision made. I think the duration of the benefit is a separate one.

I like -- I mean, from the experience of my own, in terms of TMS studies with TMS for a depression setting, for example, the same was true at the time of approval. What was known was the acute benefit. It was not known, the duration of effect at all, and appropriate postmarket approval studies were able to capture that, and with that, lead to improvements in the protocol.

I think that this is no question, an important issue, but it has to do with the focus of the indication, and the design of the study comes from that.

DR. JENSEN: Thank you.

Dr. Johnston?

DR. JOHNSTON: Hi. Yeah. I was hoping to follow up on Dr. Dorsey's question. You presented a lot of comparisons to us, and I was hoping that if you could either tell us now or tell us after the break which of those comparisons were adjusted for, for multiple comparisons? If you could share those data with us.

Yeah, go ahead.

DR. LAVIN: Hi. None of the comparisons were adjusted for multiple comparisons.

DR. JOHNSTON: Okay, thank you.

I also, I do not have the statistical analysis plan in front of me. Could you just remind me, were the primary outcomes evaluated as continuous measures or ordinal measures?

DR. LAVIN: The ADAS-Cog change from baseline was evaluated as continuous. That was both at week 7, as the primary, and week 12 as the secondary. And in terms of the

CMIC, that endpoint was looked at from a, from both perspectives of a continuous endpoint as well as an ordinal endpoint. But in the original analysis plan, it was done ordinally.

DR. JOHNSTON: Thank you.

And then just one other clarification question. One of you had spoken about the excellence of the 10% loss to the primary outcome. I wondered if you could remind me, what proportion of patients did you build into the sample size calculation for loss to follow-up?

DR. LAVIN: We built in an allowance of approximately 10% for losses to follow-up in the original plan.

DR. JOHNSTON: Thank you.

DR. JENSEN: Dr. Ellenberg.

DR. ELLENBERG: Thank you.

For clarification purposes, in our evaluation of the non-pivotal study data, could you tell us whether there was a wide range of differences amongst the non-pivotal study protocols, whether you were involved in supporting it, were they using your protocol, etc.?

MR. BAROR: Yes, thank you.

So Moran Ploznik, please.

MS. PLOZNIK: Hello. Thank you for the question.

The different studies were quite similar in the treatment protocol. They all employed 6 weeks treatment protocol. Some of them had some variances in terms of the following treatment. Most of them had similar treatment protocol, similar follow-up, and mainly the same population of mild to moderate Alzheimer's.

There were variability, but the different -- there was some variability between the different studies, in terms of time frames and inclusion/exclusion, but in the different assessment scales, not for the primary. All of them employed ADAS-Cog, and some of them

employed CGIC. In other studies, we had some additional scales.

We were involved in some of them. Some of them were sponsored. Others were investigator-initiated, and all of them were supported by Neuronix in terms of clinical and technical support, such as providing the protocol for the Korean study, for example. We provided the U.S. pivotal study protocol as a reference, and we provided technical support. We also provided training for how to operate the device obviously.

DR. ELLENBERG: So would it be fair for us to conclude that other than the time differential, this was essentially a continuation or part of an original pivotal study?

MS. PLOZNIK: To some extent, yes.

DR. ELLENBERG: Okay.

MS. PLOZNIK: With ADAS-Cog or with cognitive studies, it's obviously a little bit -- the differences in timelines are significant, and also if -- in the early study we also did some maintenance treatment procedures in some of the study so, but basically all employed the 6 weeks.

DR. ELLENBERG: Thank you.

DR. JENSEN: Thank you.

So we're going to go Dr. Lyden, Dr. Duff, Dr. Bell, and then if we have time, we'll get to the rest of you, so --

DR. LYDEN: Two quick questions. First of all, outside of the U.S. pivotal trial, not counting that one, how many seizures have occurred in patients, either in other trials or worldwide in the experience so far?

MR. BAROR: That's easy. Zero.

DR. LYDEN: Thank you. And the second question is the U.S. pivotal trial was finished, according to the timeline, and I might have gotten this wrong, in March of 2016, so quite some time ago. And given the robustness of your subgroup analysis, and given your

powerful belief in the therapy, I'm just curious, if you had done a second study using the less than 30 and the 12 weeks and all the different things you learned, you'd be done by now, and we'd have an answer. So I'm just curious if maybe that wouldn't have been the better strategy.

MR. BAROR: Running a -- let's go, first of all, on the timeline. So the data was available in March of 2016, and we made our original FDA submission in November of 2016. And we had our first meeting with the FDA back in July, if I remember correctly, of 2017. Now, these are timelines that were not so much in the control of the company.

Running another study, obviously, takes considerable amount of time and several years, and then we have -- believed then we have accumulated more supportive data since then, as Dr. Pascual-Leone has shown, with the support, for example that, of a new study coming of the Korean. That was an identical with the same indicated population. And thus we believed that there was robust enough data to follow this all the way to the clearance.

DR. JENSEN: Dr. Duff.

MR. BAROR: Just one second. Another point, please.

Moran Ploznik.

MS. PLOZNIK: Just wanted to state, the average recruitment rate for Alzheimer's studies is somewhere between 0.5 to 1 patient per month per site. So these are very long studies. So I don't think we would have done -- complete a study by now, but --

DR. LYDEN: Just do more sites.

MS. PLOZNIK: Hmm?

DR. LYDEN: Just use more sites.

MS. PLOZNIK: It has its own cost in the data in terms of reliability, but yes, more sites is another option.

DR. DUFF: I just wanted to clarify, the indication that you're proposing is ADAS-Cog

≤ 30, but it's not actually that, is it? There's a lower limit on that? Is it between 18 and 30? So a 12 point range on the ADAS-Cog is the proposal?

MR. BAROR: Yeah, 17 to 30.

DR. DUFF: Which would equate to about 3 points on the MMSE.

MR. BAROR: Lon, do you want to answer?

DR. SCHNEIDER: Yes. Yeah, yes.

MR. BAROR: Right. Okay, right.

DR. DUFF: So in the 15 years or so that I've been taking care of patients with dementia, I've never known any clinicians that use the ADAS-Cog in their clinical evaluations, outside of a clinical trial. So I just think it's going to be very challenging to actually identify patients that would be appropriate if this indication were to go forward. I wonder if you could sort of comment on how we could actually use this to identify, or how you would go about identifying such patients if this indication were to go forward.

MR. BAROR: Yes. Moran Ploznik, please, on the plan going forward.

MS. PLOZNIK: Thank you.

We are committed to provide this training to the centers. Obviously, we didn't have to provide this training for the expert raters in the U.S. pivotal study, because they had a lot of experience, but we are committed to provide this training. We know of third-party vendors that do this training. We used it in Israel for the commercial settings, and it works quite nicely.

DR. DUFF: The training's helpful, but we're talking a very narrow range of people that would be appropriate if this indication were to go forward. That's my concern, is that this a hard to identify group of individuals that are between normal and what seems to be mild cognitive impairment.

DR. JENSEN: So there'll be opportunities later on in the afternoon to go into that

some more. I want to get -- we're almost going to -- running out of time. So what I want to do is I want to have Dr. Bell ask her question. And I do want our Patient Representative to have an opportunity to ask the question. So I'm sorry if -- everybody, just write your questions down.

DR. BELL: Don't go. You could have stayed at the podium. Dr. Knopman asked my other questions, so I'd like to go back to the practical application of this. I understand about the difficulty identifying the subset of patients who would benefit, if possible, from this. But I'm still -- is there a way you can give us a practical idea of how you see this being used in the real world, in the U.S.?

DR. PASCUAL-LEONE: I'm Alvaro Pascual-Leone, and I guess I'm up to answer.

So, first of all, I think you'll hear later today from the implementation of the ADAS-Cog in Australia, in the clinical setting. And so while I agree with Dr. Duff that it is not usually a tool we use in the clinical setting, it can be used. And, obviously, appropriate training is appropriate, and it's being successfully used in Australia for that purpose.

After an initial evaluation that would include the ADAS-Cog, the patients would come to a clinic to get the intervention, would be assessed every day, because of the motor threshold determination, and in doing so, also assessed in terms of how they're doing, both cognitively and in terms of capturing potential side effects. And then they would have daily sessions every day for 6 weeks. That is what is being done for TMS for depression, for TMS for the other indications. It is, as Dr. Sabbagh was pointing out, a commitment from the family and the caregiver to bring the patient in.

What we have found in the study consistently and across the other studies is, as Dr. Sabbagh was mentioning, that patients actually rather enjoy it because it provides an opportunity to interact and to come out and to get a benefit, sure, no doubt from that alone.

DR. BELL: So it would be the same way it was done in the study design? They would need a fresh MRI before they could get the treatment planning?

DR. PASCUAL-LEONE: Thank you. That's a very good question, if I may address that.

From the experience with other indications of TMS where neuronavigation is used, one of the challenges to guide neuronavigation from conventionally accessed or clinically obtained MRIs is that they may not have all the markers that are needed. The ears oftentimes are cut off. The nose oftentimes is cut off.

Is that is not the case, if the patient has an MRI that contains that, those, the measures, then that MRI can be used. Otherwise, there is a need for an MRI. Yes.

DR. BELL: And then the last thing, since I've still got the light on, in the BI Deaconess study, the people were only -- the subjects were only looked at, at the end of the intervention. Were they looked at later, as in this post hoc analysis?

DR. PASCUAL-LEONE: Yeah. No. Thank you for that.

No. The study was just focused on the acute effect. And the reason for that is because we were looking primarily at whether the learning curves, the performance during the 6 weeks is different with the priming of the TMS or not. It was not an efficacy trial of the intervention but rather more mechanistic. We were looking also at how brain plasticity mechanisms, as measured with MRI and with TMS change in the different subgroups, and wanted to capture more mechanistic insights in the learning curve effects, including the question of domains of cognition that may be differentially affected.

DR. JENSEN: Thank you.

I would like Mr. Taylor to have an opportunity to ask the Sponsor a question.

MR. TAYLOR: Thank you. I'm the Patient Representative, so I'm a layman. I'm not a neurologist, and I just want to ask a qualifying question.

The currently approved drugs for Alzheimer's, the cholinesterase inhibitors, etc., are

characterized by we laypeople as simply slowing the progression of the disease, slowing cognitive decline. Is it fair to say that your treatment will reverse or slow cognitive decline?

DR. SABBAGH: Marwan Sabbagh, Cleveland Clinic.

The short answer is, this is a symptomatic treatment, much like you would consider a cholinesterase inhibitor. So the perception is that it would improve the symptoms for a period of time, but not necessarily change the overall trajectory, or we cannot determine that yet because that hasn't been done. But the acute effects are real, and that it would be kind of in the same symptomatic framework as you would consider other approved drugs.

DR. JENSEN: Thank you very much. So it's now 10:15. We're going to take a 15-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. And we will resume at 10:30 for the FDA presentation.

(Off the record at 10:15 a.m.)

(On the record at 10:30 a.m.)

DR. JENSEN: All right, everybody, could we please get back to our seats? It's 10:30. We're going to stay on time. It's now 10:30, and I'd like to call this meeting back to order. The FDA will now give their presentation.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel chair. FDA will also have 90 minutes to present.

FDA, you may now begin your presentation.

MS. KEEGAN: Good morning, everybody. My name is Erin Keegan, and I'm a biomedical engineer and lead reviewer in the Division of Neurological and Physical Medicine Devices at the FDA.

We welcome you to this meeting of the Neurological Panel of the Medical Devices

Advisory Committee to discuss the premarket de novo request of the neuroAD Therapy System.

Briefly, I would like to acknowledge the complete review team for this submission. Their names are on the slides.

The scope of this meeting is focused on gathering panel input on the list of specific questions that I will read in the next few slides. What may be a little different, this is not a voting panel. As such, we are not requesting yes or no votes. Instead, we are interested in the discussion and resulting panel conclusions surrounding these questions. We will incorporate your feedback into the review as we make a decision regarding the marketing status of the neuroAD in the United States.

This afternoon, the Panel will be asked to discuss and make recommendations on the questions presented here. These are all presented in the context of the device being considered as an adjunctive treatment for Alzheimer's disease, as it was studied in the clinical trials.

The questions are as follows:

1) Whether the U.S. pivotal study demonstrates a clinically meaningful benefit for the neuroAD as an adjunctive therapy.
2) When the neuroAD is used as an adjunctive therapy, the Panel will be asked to discuss and make recommendations on what amount of improvement in ADAS-Cog alone is clinically meaningful, as well as the minimum amount of clinically meaningful improvement in the CGIC.
3) Whether the ADAS-Cog ≤ 30 population is a clinically plausible subset and whether patients can be screened using this ADAS-Cog for the neuroAD.
4) Whether the post hoc identification of the ADAS-Cog ≤ 30 population at a later time point, when no treatment is given, is an adequate analysis of the pivotal

study data, in concert with the supplemental data, to demonstrate probable benefit.

Number 5 here is new.

5) Are the risks for the neuroAD adequately reported and characterized?

And finally,

6) Whether the probable benefits to health outweigh the probable risks.

During the FDA presentations, you'll hear from myself, our clinical reviewer, Dr. Claudette Brooks, and our statistical reviewer, Dr. Laura Thompson. First, I will provide an overview of the submission, including clinical and regulatory background, a description of the device, and the proposed intended use. Dr. Brooks will then discuss the clinical evidence submitted by the company. Dr. Thompson will discuss statistical considerations that give rise to FDA uncertainty and the post hoc analysis that the company has presented. Finally, Dr. Brooks will conclude the FDA presentations by providing an overview of the FDA benefit-risk assessment for the Panel to consider.

Again, as this morning, after the FDA presentations, the floor will be opened for panel questions to FDA.

Me again. In this next presentation, I will present background information to support the clinical and statistical discussions that follow. This will include regulatory information on the de novo submission pathway, a brief clinical background of Alzheimer's disease, and the landscape of FDA-approved therapies, and finally, an FDA overview of the device description.

A device is eligible for evaluation in a de novo when it does not fit into an existing device regulation, meaning that compared to other devices, it has either a new intended use, presents different questions of safety or effectiveness, or presents different risks to health. The device also needs to be considered low to moderate risk.

Based on FDA's review, the neuroAD is appropriate for the de novo pathway because it presents a moderate risk profile, and FDA is unaware of a legally marketed device that would enable an appropriate comparison of technology and indications for use.

If granted, the FDA believes the neuroAD is a Class II medical device. In the regulatory framework, this means that granting the de novo would enable the neuroAD to be used as a predicate device in the 510(k) pathway. In other words, this is a precedent-setting device and submission.

This morning you heard the Sponsor mention the idea of a pre and postmarket balance. To clarify, postmarket studies are not intended to address premarket questions. As you will hear throughout our presentation, we have premarket questions in this case. In particular, we have concerns that the benefits of the device have not been sufficiently characterized, which should occur prior to marketing clearance.

Finally, an important point to keep in mind when reviewing de novo applications, and therefore to consider throughout the presentations today, is the idea of a benefit-risk assessment. The FDA guidance document on this slide discusses factors to consider when assessing for benefits and risks. Today Dr. Brooks will provide the current FDA summary of the benefit-risk assessment as the final part of the FDA presentation.

FDA understands the debilitating nature of Alzheimer's disease and is dedicated to ensuring medical devices to treat AD have a reasonable assurance of safety and effectiveness. With this in mind, we would like to reiterate some information from this morning.

Alzheimer's dementia, or AD, is the most common dementia in the United States and worldwide. It is a progressive neurodegenerative disorder that impairs memory, thinking, language, and behavior. The most common and often earliest clinical symptom is selective memory impairment. Patients in early stages can also exhibit impairments in executive

function, judgment, and problem solving.

Neuropsychiatric symptoms can include apathy, disengagement, or irritability. Behavioral symptoms typically occur in more moderate to severe states of the disease and can include aggression, wandering, and various psychotic manifestations. The most common risk factor for Alzheimer's disease is age, particularly in those over age 65 or older.

The development of AD treatment has been focused on maintaining mental function, managing behavioral symptoms, and altering the rate of disease progression. There is no cure for AD. It is important to note that the pharmacological treatments shown here may mitigate some of the symptoms of AD for what appears to be a limited amount of time in mild to moderate stages.

These interventions do have side effects. The most common include nausea, vomiting, diarrhea, fatigue, and weight loss. While side effects for these medications are generally considered mild, the side effects of these approved drugs may be intolerable or difficult to manage in some patients. There are no devices intended to treat Alzheimer's dementia approved for use in the United States.

As we just discussed the approved AD pharmaceuticals, we take this moment to briefly discuss the Sponsor's promotion of a comparison between the neuroAD and approved drugs with respect to determining an MCID on the ADAS-Cog scale.

This morning the Sponsor cited the ADAS-Cog changes from baseline as well as other assessments and endpoints, and compared the magnitude of those numbers to the mean ADAS-Cog changes in the U.S. pivotal study. From this slide, you can see there are vastly different regulatory approval standards between pharmaceuticals and devices, which should be taking into account when driving this comparison.

While Dr. Brooks will go into more detail on this slide in the benefit-risk section, the main takeaway here is that the approved drugs we just listed were not approved because of

their change on the ADAS-Cog. They were approved because they showed a statistically significant difference between active and placebo on global and cognitive co-primary endpoints. Therefore, using the magnitude of the changes in ADAS-Cog seen in the approved drugs does not inform an MCID on the ADAS-Cog scale because those magnitudes of changes alone would not have supported approval.

With this background in mind, we now turn our attention to the neuroAD, beginning with the regulatory history between FDA and Neuronix. As you can see, from 2010 to 2014 the FDA and the company held a series of pre-submission interactions to discuss the design of the pivotal study. Please note that because of the anticipated risk profile of the study, it did not require FDA oversight, and IDE regulations did not apply.

The Sponsor submitted a request for designation through the Expedited Access Pathway program in 2016. We granted that designation, which means we recognize that a device treatment for AD would represent a breakthrough device intended to address a currently unmet need. However, it is important to note that FDA granted the designation based on the potential of the neuroAD as a device treatment for the disease. The designation was granted before the results of the pivotal study data were available. For reference, the EAP program is now included in the Breakthrough Devices program.

The company submitted the de novo in November of 2016, and we formally requested additional information in early 2017. This request was focused on the clinical data. We held a meeting with the company to discuss approaches to addressing the clinical deficiency in the spring of 2017, and the company submitted the complete response in the fall of 2017.

As part of our final review, we requested external input via the Network of Experts program. This approach is less formal than a panel homework assignment, and we did not discuss the particulars of the submission or the data. Instead, we requested input on the

clinically meaningful change on the ADAS-Cog scale, the scale used to assess primary effectiveness in the neuroAD trials.

We ultimately denied the de novo application in June of 2018. This was based on our high level of uncertainty in the clinical evidence that was presented and on the grounds that the totality of the evidence does not support a clinically meaningful benefit that would outweigh the probable risks. The Sponsor appealed this denial decision, and the submission has been reopened to incorporate panel input before a final decision is rendered.

As you heard this morning, the neuroAD system is a device system intended as an adjunctive therapy for the treatment of Alzheimer's dementia. The proposed IFU is listed here. An important note on this indication from the FDA perspective is that the Sponsor intends to use the ADAS-Cog assessment scale for patient selection of their device. This proposal is based on a post hoc subgroup finding.

Again, because you heard a device description this morning from Neuronix, we would like to highlight just a few points. With respect to the TMS aspect of the device, in the neuroAD, as in the marketed TMS indications, the TMS intensity is patient-specific. The intensity of the TMS is determined using the patient's daily motor threshold, which is determined by applying single pulse TMS to the motor cortex and monitoring for a motor reaction. The intensity at which a motor reaction occurs is then used to set the therapy intensity of the magnetic stimulation.

With respect to the cognitive training aspect of the device, these tasks have a scale of difficulty levels that automatically update based on performance according to an algorithm developed by the Sponsor. It is important to note, the impact of increasing or decreasing the difficulty level of the cognitive training in the active group throughout the study was not a variable that was prespecified for assessment. Therefore, this information has not been requested by or presented to FDA. The impact of increasing or decreasing the

cognitive training on the results of the pivotal study is not clear. We note the treatment paradigm on the next slide.

This slide illustrates the treatment paradigm, and we call attention to the following aspects:

- The TMS and cognitive training is delivered concurrently.
- The full treatment session for the neuroAD will last 6 weeks, as shown in the bottom of the slide.
- An example for the first week is blown up and shown in the figure.
- For each week, the six brain regions are targeted on alternating daily schedules.
- Each daily treatment session is conducted in a clinic and lasts about 1 hour. The patient must return to the clinic 5 days/week for 6 weeks to complete 1 treatment session.
- The pivotal study was designed with this same 6-week treatment paradigm. The primary effectiveness assessment in the pivotal study occurred at week 7, one week after the end of treatment.

Finally, before we begin to discuss the clinical evidence that the company has provided to FDA, we would ask that you keep the following points in mind. The FDA considers the prespecified results of the pivotal study to be the primary dataset. While we have considered the supplemental datasets and the post hoc analyses because the Sponsor has provided them, these carry high uncertainty. All post hoc analyses that are presented by Dr. Brooks in the next section were conducted by the Sponsor and not by the FDA.

Throughout this presentation we have made the decision to keep the nominal p-values for the sake of discussion. However, all p-values except that which were calculated for the primary, prespecified endpoint are nominal p-values. We try to call attention to these throughout the presentation.

Now I would like to introduce Dr. Claudette Brooks, who will be discussing the clinical evidence that has been presented for the neuroAD.

DR. BROOKS: Good morning. I am Claudette Brooks, neurologist, medical officer, and clinical reviewer in the Division of Neurological and Physical Medicine Devices at the FDA.

Looking at the outline, I will discuss clinical evidence and the FDA's perspectives on elements of the clinical trial design of the pivotal study, or the U.S. pivotal study, the study's results, the post hoc analysis subgroup, additional post hoc analyses that involve two studies from Korea, as well as other supplemental investigations submitted by the Sponsor to us.

During the discussion of the pivotal study, we would like to highlight some of these specific points. Again, the pivotal study, referring to the U.S. pivotal study, was the largest, most scientifically rigorous, and most complete dataset the Sponsor provided. The pivotal study did not meet its primary effectiveness endpoint. Sham outperformed the neuroAD's performance.

The safety data from the pivotal study is consistent with similar Class II devices. The design and conduct of the pivotal study did not raise significant concerns as far as its prespecified form and statistical analysis plan. The study results and the analysis of the data did raise uncertainty regarding the reasonable assurance of effectiveness and possibly safety of the device in this patient population.

The formal name or designation of the pivotal study is the NRX-US4: Effect of NeuroAD, Combined TMS Stimulation and Cognitive Training on the Cognitive Function of Mild to Moderate Alzheimer Patients. Thus, the study was designed for mild to moderate Alzheimer's patients. For brevity, as I've been referring to it, it is the pivotal study or the U.S. pivotal study. And you'll see why sometimes we put U.S. in front so we don't confuse

you with another study that we will discuss.

This was a prospective, randomized, multi-center, double-blind, sham-controlled clinical trial. It included 10 total study sites, 9 in the U.S. and 1 in Israel. Patients in the study were randomized to two groups, active and sham, as you all have heard. While there are two distinct active therapy components, TMS and cognitive training, the study did not assess these components separately. And that was also discussed by the Sponsor earlier.

Also, as described, the active group received real TMS and real cognitive training; sham group, sham TMS and sham cognitive training.

This device was studied as an adjunctive to pharmaceuticals. Therefore, it is important to note that the results shown already take the adjunctive nature of the system into account.

The Sponsor has already described the endpoints in the pivotal study, and you all have probably read them a few times, so I won't go into them right here, but we should highlight the following. This cohort that we're going to discuss first includes all eligible study patients. No active or sham treatment was delivered after week 6. Endpoints assessed at 7 weeks were approximately 1 week post-treatment, and endpoints assessed at 12 weeks were approximately 6 weeks post-treatment. Twelve-week secondary endpoint time point was recommended by FDA to the Sponsor as an assessment of treatment durability in those early discussions that Ms. Keegan described to you a few minutes ago, not as a discrete effectiveness endpoint in itself.

Two assessment scales used for the study were the ADAS-Cog and the CGIC, which have been discussed already. Looking at it by the 70-point scale of ADAS-Cog, it is important to note that by convention, a negative change in the same represents improvement.

CGIC is a 7-point scale where a 1 indicates very much improved; 4, no change; and 7,

very much worsened. For purposes of assessing an intervention, it is important to note, again, that 4 on the CGIC scale indicates no change.

Looking at this graphic in this slide, the pivotal study was designed to contain elements that reduce uncertainty in the results, including a prespecified statistical analysis plan, a blinding assessment, a plan for handling missing data, poolability testing and covariate analysis.

As depicted in the figure, populations were defined as the primary safety. There were the 20 run-in patients that were previously described, and they were evaluated in the primary safety population only. They were not included in the primary efficacy. The primary efficacy, which included the randomized patients who had a baseline ADAS-Cog score and least one treatment visit, whether they were active or sham, and the per protocol population, which filtered the primary efficacy population patients according to some prespecified criteria. We will focus on the primary safety and primary efficacy populations only.

Looking at patient disposition, for the 109 randomized patients here, as I wanted to note that there were three patients that were not included in the primary efficacy population due to protocol deviation and software error, making the primary efficacy population an *n* of 106 on this chart.

As we present the results of the clinical data, it is important to keep this disposition chart in mind. In our figures we try to provide the total amount of patients that contributed to the specific results that we are presenting. As we look at different time points and subgroups, the total number of patients does vary. However, we have no concerns with the patient accountability in the U.S. pivotal study.

Once again, please note, the patients in the pivotal study only received one course of treatment. And also just I want to note to you, in our figures for most of them, patients

who've received active treatment are in blue, and patients that received sham treatment are in red, just to make it easier for you all to follow.

Next slide, we are going to talk about the pivotal study, and the reporting of adverse events, or otherwise known as AEs. They reported all AEs, as they stated, whether they were they were associated with the device or procedure. We focus on AEs that were related in this slide, as similar to a slide that was presented earlier to you this morning.

The rate of pivotal study patients experiencing any definite, probable, or possible study procedure or device-related adverse event was 14% in the active group and 4% in the sham group. That active group also included the run-in patients. The 11 active group patients reported 15 events total that were found to correlate with relatedness to the device or the procedures. Those AEs reported for the U.S. pivotal study that were deemed related to the device or treatment as determined by the site investigator were primarily mild. The TMS device in general is considered a moderate risk device, and part of this is due to the possible seizure provocation.

At the primary effectiveness endpoint, the sham group outperformed the treatment group with a mean difference between groups of 1.45 in favor of the sham. The figure on the left shows the mean difference from baseline of each group. On the right, we see the mean baseline score and the mean score at 7 weeks for the active and sham groups on the full 70-point scale of the ADAS-Cog.

CGIC, which were secondary endpoints, and were prespecified at 7 and 12 weeks, at 7 weeks the CGIC for sham and treatment are both near 4. Remember, on the CGIC scale, 4 means no change. At 12 weeks, the CGIC favors treatment a little more, but still near no change. Both minimally favored treatment with a mean change from baseline CGIC that was less than half a point.

For the first time in this presentation, we will present nominal p-values as my

colleague described earlier. There are p-values that are listed here and in some subsequent slides for the sake of completeness and discussion only. P-values in secondary and post hoc analyses should be viewed with caution, considering that the study did not meet its primary endpoint.

Change from baseline in the ADAS-Cog at 12 weeks was also the final prespecified secondary endpoint. The Sponsor did not originally intend to include this in their study, and FDA suggested it for looking at durability, as I said earlier. At 12 weeks, the mean difference in ADAS-Cog from baseline to 12 weeks was -0.42, or 0.42 in favor of the treatment group. As in the display of the primary endpoint results, figure on the left, mean difference from baseline of each group. On the right, we see the mean baseline in comparison, active and sham, on the full ADAS-Cog scale.

In summary of the pivotal study prespecified results, the study did not meet its primary effectiveness endpoint. While in the other studies this has usually meant that merely did not reach statistical significance, in this case the sham group outperformed the treatment group. ADAS-Cog at 7 weeks was compared to baseline, sham outperformed treatment. At 12 weeks, the difference in ADAS-Cog began to trend in favor of the treatment group. The patients did not receive any neuroAD or sham treatment between 7 and 12 weeks.

We can only speculate as to the causes of these observed results. There may have been a delayed response to treatment in the active group, active group patients may have improved once treatment was ceased, or something else not fully understood or defined as of yet.

From here, we will discuss other analyses that were not prespecified in the U.S. pivotal study. All of these were post hoc.

At the FDA, we generally have the most confidence in prespecified analyses.

However, we can and do review the results of post hoc analyses even though they carry greater uncertainty. These types of post hoc analyses are generally considered to be exploratory and hypothesis-generating.

In the Sponsor's case, they did pre-specify an analysis of an impact on disease severity at baseline as a covariate. However, they did not pre-specify the hypothesis that it would represent an independent cohort that demonstrates a larger and more consistent treatment effect. In other words, despite the interaction test being prespecified, the Sponsor's intention was to make a claim for the effectiveness of the neuroAD over sham for the entire population.

Changing the intended population after analyzing the data and finding that the overall test was not significant amounts to a post hoc hypothesis test. Consequently, analyses associated with the group defined by baseline ADAS-Cog ≤ 30 carry much greater uncertainty.

Looking at this, the patient level data, the subgroup enhances the effect in the active group and lessens the effect in the sham group. Here, we can look at exactly which patients are included and excluded if the cutoff is ADAS-Cog is less than or equal to 30 in those patients in the pivotal study. Each patient's response from baseline is shown as a single bar at both 7 and 12 weeks. Filled bars are patients whose baseline ADAS-Cog is less than or equal to 30.

I just want to note, these are blue and red here. In your packs, they may be purple and green, if that's throwing you all off. Okay, because I saw some -- okay.

And these results are included in the post hoc analysis. Empty bars are patients who ADAS-Cog is greater than 30 and whose results do not count towards the post hoc analysis. The majority of the cohort of patients with ADAS-Cog score greater than 30 appear to be poor performing active patients, in essence, positive changes on the ADAS-Cog scale, and

high performing sham patients, negative changes on the ADAS-Cog scale.

Based on this view of the data, it appears that limiting the data to only those with a baseline ADAS-Cog score less than or equal to 30 would influence the results in favor of the treatment from both the active and sham eliminations.

At the 7-week time point, the ADAS-Cog mean scores in this post hoc subgroup continue to favor the sham group, but by a smaller margin of 0.47 points. We're looking at the post hoc. Now we're looking at the post hoc.

At the 12-week time point, the mean difference in the ADAS-Cog scores between the active and sham groups favors treatment group by 1.61 points.

As we mentioned previously, we have concerns that this was shown at 12 weeks in the absence of treatment from the 7-week assessment. We have concerns about the methods used to generate this result. And in addition, we believe that this result can be attributed to the -- if we can believe this result can be attributed to the neuroAD, we have questions regarding the clinical meaning of the 1.61 difference between the groups.

The Sponsor also provided the results of the CGIC for the post hoc baseline ADAS-Cog ≤ 30 subgroup. In the post hoc subgroup, the CGIC at the 7-week time point resulted in a difference of 0.07 in favor of treatment. At 12 weeks, this difference reaches 0.40 in favor of treatment group. The 0.40 difference at the 12-week time point is the highest magnitude CGIC difference in favor of treatment in the post hoc U.S. Pivotal subgroup. This is in the absence, again, of any treatment during those intervening weeks.

The Sponsor submitted additional analyses intended to support the results of the post hoc analyses of the U.S. pivotal study and the post hoc change of the population to those patients with ADAS-Cog ≤ 30. The Sponsor contends that these studies, including the post hoc analysis of the Korea 1 study, also known as the Korea pilot, and the results of the Korea 2 study, also known as the Korea pivotal, and the meta-analysis with the U.S. pivotal

post hoc subgroup confirm their ADAS-Cog cutoff and reasons for the proposed indication for the neuroAD. We will present the data as reviewed.

Looking at the overview of the Korea designs, they had some similarities to the U.S. pivotal, 6 weeks intervention, 6 weeks follow-up, no further treatments between week 6 and 12. The primary endpoints were safety, and the ADAS-Cog at 7 weeks compared to baseline relative to the change in the sham group. Secondary endpoints included the CGIC and Neuropsychiatric Inventory. Both of the Korea studies have small sample sizes of patients as well.

Korea 1 was a pilot study that did not limit the population, so there are patients in that study that are above and below 30. Korea 2 was intended to be a pivotal study for the Korea FDA that followed the Korea 1 pilot. However, this study was stopped with 22 patients enrolled and is pending U.S. FDA's decision before resuming the study. As such, these results should be considered interim.

Please note, as you saw this morning, because the protocols were similar among the three studies, the Sponsor appears to assume that the studies could be considered exchangeable and therefore could be included together within a meta-analysis.
Dr. Thompson will provide more information about the FDA's concerns about this in a few minutes.

Here we present the ADAS-Cog results of the Korea 1 study. Korea 1 enrolled patients with mild to moderate AD, similarly to the U.S. pivotal. Results of the Korea 1 at 7 weeks and 12 weeks for both entire cohort and post hoc analysis subgroup are presented here. So as a reminder, Korea 1 involved above and below 30, initially.

On the left is the original overall study population, and the right shows the post hoc subgroup. While we recognize that there are only 5 patients in the study with ADAS-Cog > 30, the overall population outperforms the post hoc study subgroup, which is opposite of

the pivotal study. Unlike in the pivotal study, the maximum differences are noted at 7 weeks and not 12 weeks.

Looking again, the performance of the ADAS-Cog in the less than 30 subgroup, between Korea 2 and the U.S. pivotal, that's the U.S. pivotal. Note, ADAS-Cog scores below or equal to 30 were not a post hoc subgroup analysis for Korea 2. That study was designed to take patients below 30. So that is its study results to date. As I stated, it has been put on hold.

Please note the trend in differences in the Korea 2 and the U.S. pivotal post hoc analysis subgroup. Both are ADAS Cog 30 or less in those two. Both are changes from baseline ADAS Cog at 7 and 12 weeks. Both studies did not give neuroAD or sham treatment during those intervening 6 weeks. Again, this decrease in magnitude of change between groups over time contrasts that seen in the U.S. pivotal post hoc analysis subgroup, which for reference is in the figure on the right.

To summarize the previous few slides, we have another figure. This figure shows the mean differences in ADAS-Cog between the active and sham groups for U.S. pivotal, including full cohort and post hoc subgroups, the Korea 1 study, full cohort and post hoc subgroup, and the Korea 2 studies. These are in different colors, not to have confusion during the different groups.

Please note that there are between-group differences and trends. The U.S. pivotal study demonstrated positive differences at 7 weeks for both full cohort and the post hoc subgroup, indicating that sham performed better. It is not clear why the two Korea studies and the pivotal study did not demonstrate similar trends, considering they used similar designs, used similar devices, a similar treatment paradigm, and to some extent, similar populations. This raises concerns regarding the validity of the pivotal study post hoc analysis and the exchangeability of these studies.

Reminder, we are currently discussing the post hoc analyses and supplemental studies. For the most part, this is not a discussion regarding the prespecified endpoints and data of the U.S. pivotal study, although we will draw attention to the prespecified data results when appropriate. Many points in this discussion are in response to some of the Sponsor's contentions regarding the data results that they submitted.

Here I'm just looking at, we're just looking at the study sample sizes and the datasets that were submitted by the Sponsor. All but one of the datasets, Harvard, was derived from patients residing outside the United States. For comparison, the sample sizes for all clinical datasets are shown at the bottom of the figure. And as these were not intended to support the neuroAD for U.S. marketing, both the safety and effectiveness data from these studies is sometimes incomplete.

For example, some of the Assaf studies did not have raw safety data for FDA analysis. Furthermore, ADAS-Cog results are presented in ranges of 6 to 10 weeks and 10 to 14 weeks because follow-up did not always align with the 7- and 12-week follow-up of the U.S. pivotal.

Finally, the ADAS-Cog data is not accompanied by CGIC results in most cases. This variability in reporting and missing data decreases reliability.

If you would like to look at the pooled analyses that were done by the Sponsor, please refer to your panel pack. Because the validity of pooling these studies is not clear at this time, we would like to highlight the patterns noted in the studies that had both assessment time points to demonstrate how these also contributed to our overall uncertainty in the data in the treatment effect.

These six studies are highlighted in particular because we were provided the mean difference in ADAS-Cog at both the earlier and later assessment points. While the post hoc U.S. study subgroup does trend in favor of treatment from 7-12 weeks, it is the only study

or subgroup that appears to do so.

Because it may appear from the supplemental studies that there's some consistency in the trend between 7 and 12 weeks, even if it differs from the post hoc U.S. pivotal study, this slide is intended to give additional context. In this slide we show some studies with the same mean differences between groups over time but we present the sham and active contributions.

We can see that while the magnitude of the between-group differences decreases over time in all but the pivotal study post hoc analysis subgroup, the underlying data demonstrate inconsistent trends across studies. In some cases, the sham is doing much better over time while in others, the treated patients are either holding steady or doing slightly worse. Because of this variability, we do not think that this data lent any support to the post hoc results of the pivotal study, U.S. pivotal study.

To summarize, the clinical dataset carries high uncertainty. With respect to device effectiveness, in the most robust prespecified assessment the results favored the sham devices. The post hoc analysis of the pivotal group is hypothesis generating because the results of the study were known when this subgroup was chosen.

Supplemental analyses do not lend support to the post hoc analysis because the baseline ADAS-Cog cohort or the trend from 7 to 12 weeks was not shown in the Korea studies or the supplemental investigations.

With respect to safety, the pivotal study data appears consistent with a moderate risk device. The supplemental datasets offer incomplete safety data.

Now I will turn it over to Dr. Laura Thompson who will discuss statistical considerations.

DR. THOMPSON: Thank you, Dr. Brooks.

Can you even see that? My name is Laura Thompson. I am a mathematical

statistician in the Division of Biostatistics, Office of Surveillance and Biometrics.

I will be discussing statistical considerations but also looking a little bit into more detail regarding the data themselves.

So this is an outline. I'll start with a review of the study design and primary endpoint, showing results on the ADAS-Cog over assessment times, by group. I will also address the interaction test between baseline ADAS-Cog and treatment group on change from baseline, including what was prespecified about the test and what that means with respect to reliability of subgroup results.

I will describe FDA's concerns about the uncertainty of the post hoc subgroup results, including that the specification of the cut point of 30 was done after results were known, which can lead to spuriously high findings, and that the cut point of 30 comes from a measurement instrument, which may have error. Finally, I will make some comments on the Sponsor's meta-analysis.

In my presentation, I will deal with certain aspects of the study. These include the primary endpoint and the interaction. This interaction is what prompted the post hoc subgroup.

For the study design, the primary endpoint was change in ADAS-Cog at 7 weeks. A 12-week assessment was recommended by FDA to measure the durability of any treatment effect achieved by the end of treatment application at 7 weeks.

A test for interaction between baseline ADAS-Cog and treatment group was prespecified. If the test was not significant, then any treatment effect found would be considered not modified by baseline ADAS-Cog score. There was no plan specified for if the test was significant.

As a review, the primary endpoint was change in ADAS-Cog from baseline to 7 weeks, and the secondary endpoint was the change at 12 weeks. In this table, I provide

the baseline means by treatment group, as well as the mean difference between groups at each time point. The mean difference at 7 weeks favors sham, point estimate of 1.45 with a confidence interval that is heavily in positive values, with a p-value of 0.09. By 12 weeks, the difference is negative, but with a small magnitude, -0.42, and a confidence interval that indicates quite a bit of uncertainty. In the next slide I provide more detail about the ADAS-Cog scores by assessment time.

So in this plot, at each of the three assessment times, on the x-axis baseline, 7 weeks and 12 weeks, I provide box and whiskers plots of the distribution of ADAS-Cog scores by treatment group in order to show variability of scores at each time point, by group. In any given box plot, the box ranges from the 25th percentile of the scores to the 75th percentile. The horizontal bar, somewhere inside of the box, gives the median, the 50th percentile. The whiskers approximate a 95% confidence interval, and the circles represent outlying values.

The distribution of ADAS-Cog scores at 7 weeks by treatment group doesn't show much difference between groups. The medians, however, indicate that the sham, which is the red box, is favored at 7 weeks. There is a small separation of the distributions between groups, favoring active, at 12 weeks, but there is still quite a bit of overlap in the distributions.

This slide demonstrates the interaction between baseline ADAS-Cog and change from baseline at 7 and 12 weeks that prompted the Sponsor to seek an indication at baseline less than or equal to 30. These are scatterplots of baseline ADAS-Cog on the x-axis by change from baseline, on the y. The left-hand side is 7 weeks and the right-hand side is 12 weeks.

Each circle or each dot in a scatterplot is one subject. Red is sham, and black is active. I also put in a vertical line at a value of 30, where the Sponsor proposes to indicate

the device. As you can see, the scatterplot, both of them don't appear to show strong patterns between treatment groups at either 7 or 12 weeks. But if you calculate the mean changes from baseline by treatment group at 7 weeks and 12 weeks, where again, the red box is sham and the black is active, you can see the observed evidence of interaction where at 12 weeks the active group outperforms the sham on average at baseline ADAS-Cog ≤ 30, but for baseline ADAS-Cog > 30, sham outperforms active.

The crossing lines at 12 weeks is evidence of a qualitative interaction, where the active is effective in one subgroup, but the sham is effective over active in the other subgroup. This can be compared to a quantitative interaction, where the trend is the same in each subgroup, but larger in one subgroup over the other, as it is for week 7 where the sham outperforms active in both of those subgroups. True qualitative interactions are commonly thought to be fairly rare. And the evidence for the subgroup is found within such an interaction.

This slide summarizes what the previous slide showed but also includes confidence intervals. The subgroup of baseline ADAS-Cog ≤ 30 is in the top rows, and its complement, baseline ADAS-Cog > 30 in the bottom rows. For baseline ADAS-Cog ≤ 30, at 12 weeks the result favors active, with a nominal post hoc p-value of 0.08. Note that the Sponsor is requesting that we clear the device based on this result of -1.61 at 12 weeks in the post hoc subgroup.

Note that all p-values here are not adjusted for multiple hypothesis tests; they are included for informational purposes only. As an aside, a Bonferroni adjustment would compare the p-value to say 0.05 divided by the number of analyses that were done. So even if there were 4 prospective analyses, so 7 weeks and 12 weeks in the full population and 7 weeks and 12 weeks in the subgroup, the p-value of 0.08 would be compared to a threshold of 0.013, making the .08 not as compelling.

For baseline greater than 30, the sample size is small, eight subjects in each group, but at both 7 and 12 weeks there appears to be some evidence of the device performing worse than a sham, and even worsening absolutely on ADAS-Cog over time, as the average change from baseline is positive. The next slide provides more detail regarding the distribution of scores in these subgroups.

This slide shows boxplots of ADAS-Cog scores over assessment time by group but separated by subgroup. For the less than or equal to 30 subgroup on the left-hand side, we see some separation between active and sham distributions at 12 weeks, where the distribution of active scores, which is in the blue, moves lower than that of sham scores. This corresponds to the point estimate, the mean difference of -1.61 in favor of active.

For the baseline greater than 30 subset, at both 7 and 12 weeks, the distribution of scores from sham shows separation from the active distribution, more so at 12 weeks. The sham distribution appears centered at better outcomes, and the corresponding point estimates from the previous slide are here.

My point of these last two slides is that if we are to consider that the result in the less than or equal to subgroup shows superiority despite not being prespecified and despite being tested after study results were known, then we might also carefully look at the greater than 30 group with respect to inferiority of the device over sham because neither subgroup was intended to be tested for a treatment effect.

With a post hoc subgroup that comes from an observed qualitative interaction that was not expected, it may be incomplete to highlight the part that is favorable and ignore the rest. In this case, the rest indicates that the certainty of the cut point of 30 may be important to ensure that the right patients are treated with the device. I return to the cut point later.

FDA's uncertainty with clearing the device based on the post hoc subgroup result is

summarized in this slide. First, a prespecified interaction involving a continuous covariate, such as baseline ADAS-Cog, does not pre-specify the cut point to define a subgroup. Despite any significant interaction test, and despite any literature articles claiming that less than or equal to 30 may enhance any treatment for Alzheimer's disease, the cutoff value was chosen after study results were available, making the subgroup selection post hoc.

Analyses associated with a post hoc subgroup carry greater uncertainty than planned hypothesis tests. In particular, the usual p-value or the nominal p-value may be incorrect due to using the data to generate a new hypothesis and to test it. The chance of finding a significant p-value, despite no real effect, increases with the number of tests done. The chance of finding a p-value of 0.08, given no real effect, can be as high as 28% if four tests are done.

Any treatment differences may also reflect bias in choosing a hypothesis that gives a good test result, for example, choosing to test the less than or equal to 30 hypothesis after availability of the data. Consequently, the likelihood of a good result by chance is higher when a result is highlighted post hoc, hence FDA's uncertainty in interpretation of the Sponsor's result.

In fact, several different post hoc subgroups might be identified that could separate the population into responders and non-responders, even using independently, randomly generated covariates. If the Panel would like to see an example during the Q&A session, I can show one.

There also may be uncertainty around the exact cut point for which the device may be effective, if it is effective over sham. The cut point of 30 used to indicate the population for the device contains a measurement error. It is not a naturally occurring subgroup, such as that determined by age or gender. It was derived using a measurement. In fact, a range of values around a score of 30 may be clinically equivalent to a score of 30, especially across

different sites or days. One site might score a patient 29, and another site might score one 33, even if they have a true score of 30.

As we will show later, our rough estimate of the standard error of measurement is about 3 points, indicating that a patient's score has a standard deviation of about 3 around their true score on any given administration.

When a restricted indication is based on a measurement instrument, tolerance for uncertainty may be lower in order to be sure that 30 is an appropriate value that will not prevent treatment for those who could have benefited, or recommend treatment for those who may worsen.

FDA did perform a validation of the cut point of baseline ADAS-Cog of 30 to assess whether this value could distinguish patients who respond better on active over sham on an independent dataset. And, ideally, the independent dataset should come from outside of the study.

We estimated the treatment effect in subjects with baseline ADAS-Cog ≤ 30 using supplemental studies provided by the Sponsor and compared that result to the treatment difference in the full study cohort in order to evaluate an enhanced effect in the subgroup. This is important because the enhanced effect is the premise for the U.S. pivotal study, as there was no overall effect of the device over sham. So a key question is was the enhanced effect in the U.S. subgroup merely a chance finding from the pivotal study?

The Sponsor indicated that the studies most appropriate for an external validation were the two Korea studies and the study done in Italy. These studies are in the columns of the table in this slide. In addition, we add a superset of studies that combines them, pools the Korea pilot and Italy studies together due to the very small sample size of the Italy study. I will address the first three columns in this slide.

You can see in the first row that the treatment differences in the subgroup are all in

favor of active. It's not surprising that this subgroup shows a favorable result in the supplemental studies, because in many of those studies, the entire cohort showed a favorable result. But for the Korea 1 study, the pilot, Korea pilot study, the subgroup result is a decreased result over the entire population. The entire population is a point estimate of -2.51. This study has been described as the most similar to the U.S. study, with an identical sham.

It is true that Korea 1 had very few subjects, and most were in the subgroup. However, such a decreased result over the entire population at 12 weeks was seen in the supplemental studies too, as I will show in the next slide.

Okay, this is a busy slide. It's meant to illustrate evidence of general inconsistency and treatment difference over the assessment times for the U.S. subgroup compared to the supplemental RCTs. Because of small sample sizes in the individual RCTs, I pooled them together but just to show a pattern. I mean, we've been talking about pooling maybe not being appropriate, but they all have very small sizes, and I just wanted to see, what is this general pattern going on.

So I selected the randomized control trials that used what was noted as the latest generation of the device, and a very similar sham. And so this was Korea 1, Korea 2, Assaf 3, and Italy. And their figures are on the left. The U.S. study is on the right. The subjects restricted to baseline ADAS-Cog ≤ 30 are in the top row, and the bottom row is the full cohort.

The supplemental RCTs pooled together trend toward a treatment difference that does not appear to depend on baseline ADAS-Cog. That is, the full cohort set already shows some support for active over sham, at least for 7 weeks. So the blue is lower than the red. And the support does not appear to improve after the restriction to baseline ADAS-Cog ≤ 30. However, the U.S. study shows no apparent improvement in the device over sham at

7 weeks, but at 12 weeks, the active distribution moves lower, more so for the subgroup versus the full cohort.

Despite the individual supplemental studies being small, collectively they appear to support a neuroAD effect over sham at 7 weeks, but it wanes at 12 weeks and does not appear to depend on the baseline ADAS-Cog of 30 cutoff. This creates uncertainty in the supplemental studies supporting a restricted indication.

Now, you may be thinking that this slide doesn't appear to show much of anything in terms of one treatment group being better than the other, but the set of boxplots that I circle here is what is under consideration for clearing the device. If this set is under consideration to conclude superiority of the device, then it's not clear that any other set of boxplot pairs should be ignored in terms of what it shows in comparison to what is circled in red.

So back to the table a couple of slides ago. Now I discuss Korea 2 or Korea pivotal study alone. The Korea 2 study enrolled only subjects with baseline ADAS-Cog ≤ 30. That study did yield a treatment difference similar to the other studies, -1.73. While this may seem like an independent confirmation of the subgroup effect, FDA has concerns with whether this study qualifies as a confirmation.

First, the study is incomplete. Only 22 patients have been enrolled so far. In addition, the treatment difference has substantial variability. Notice that the 95% confidence interval decidedly includes zero. Also, the pattern of results across the two assessment times are different for the two studies, U.S. and Korea 2. Specifically, the increase in treatment difference from 7 to 12 weeks that was seen in the U.S. study, despite no treatment applied after 7 weeks, was not seen in Korea 2 nor often in the supplemental studies in general.

And, finally, the Korea 2 study may not generalize to a U.S. population. It was

conducted in a different country.

To show that generally different trends over time with Korea 2 versus the U.S. study have -- the boxplots again. This slide compares the two studies' ADAS-Cog scores, their distributions over time and treatment group. The U.S. study is restricted to the baseline ADAS-Cog ≤ 30 subgroup. Korea 2 is on the left, and the U.S. study is on the right.

Whereas the Korea 2 study on the left shows indication of separation of active from sham at both 7, and to a lesser extent 12 weeks, the U.S. subgroup shows no noticeable separation of the distributions at 7 weeks, and some at 12 weeks.

The pattern shown for Korea 2 is similar to the overall pattern shown in the other supplemental studies, at 7 weeks shows an effect of active, and the effect wanes by 12 weeks. And note that these studies used the same device and an identical or very similar sham.

FDA has not been able to determine why there is a difference in results over time, in particular why the treatment difference would increase after ceasing the application of stimulation, and as such is hesitant to clear the device for a U.S. population.

Finally, the Sponsor presented a meta-analysis that included three studies, the U.S. study, Korea 1, and Korea 2. For the meta-analysis, they only included study subjects in these studies with baseline ADAS-Cog ≤ 30. The analysis assumes exchangeability among the three studies, which roughly means similarity of the studies, in terms of outcome, design, patient population. However, FDA does not agree that the Korea studies are exchangeable with the U.S. study.

First, as I noted before, results from the Korea studies show a different pattern of effectiveness of the device from 7 to 12 weeks. They were conducted in different countries. And, finally, as the Sponsor presented, there was some evidence of different average motor thresholds across the studies, which may impact response to TMS, which is an important

component of the device.

However, even if exchangeability did hold, FDA believes that all subjects in the studies should be included in the analysis. For confirming a subgroup result, FDA often recommends that the company run another study or collect new data in this subgroup. For the new analysis, we often suggest statistically combining results from the two studies, but we don't recommend eliminating the poorer performing subgroup. Instead, the poorer performing subgroup may serve as a multiplicity adjustment to down-weight potentially spurious results from the initial post hoc finding.

In the Panel pack, we show an alternative analysis to the Sponsor's meta-analysis. However, even that analysis is only applicable if exchangeability holds.

To conclude, prespecified hypothesis that are documented and planned to be tested before any examination of the data are a tenet of good trial design. Despite the interaction test being prespecified, the Sponsor's intention was to make a claim for the effectiveness of the device over sham for the entire population. The cut point was chosen after study data were available and then tested on those data. Hence, the subgroup result may be inflated, and the p-value is not adjusted for multiplicity.

Supplemental studies collectively show different patterns of treatment benefit over sham than did the U.S. study across the two follow-up assessments as well as across the less than or equal to 30 and greater than 30 subgroups. Taken together, these points lead to uncertainty in concluding reasonable device effectiveness in a U.S. population.

I will now turn the slides back over to Dr. Brooks, who will talk about the benefit-risk considerations.

DR. BROOKS: I'm back. So earlier we discussed the clinical evidence, and during that discussion, we attempted to point out our areas of concern and uncertainty and give some justifications for those concerns. Dr. Thompson has just discussed those areas from a

statistical perspective. And now we will go on to the benefit-risk perspective.

Over the next few minutes I will try to walk through how the FDA assessed the benefits and risks of the evidence presented to us by the Sponsor.

Now, this is a simplified description of the benefit-risk assessment process that review staff use in the Center for Devices and Radiological Health, otherwise known as CDRH. It begins with an assessment of the benefits, looks at the results first without considering the uncertainty in the dataset. If the results are clinically meaningful, review staff then look to determine whether the level of uncertainty is acceptable.

We evaluate the benefit first, because if the results do not demonstrate a clinically meaningful benefit, the probable reasonable assurance of benefit to health cannot outweigh the probable risks. And, remember, I said it was simplified. So looking at a review of the device effectiveness results in the U.S. pivotal study, the full cohort, sham outperformed treatment at the primary endpoint.

The treatment did outperform sham at later time points for both the U.S. pivotal full cohort and subgroup on the ADAS-Cog. The largest difference found is 1.61 points in ADAS-Cog between treatment and sham groups in the U.S. pivotal, is in the post hoc analysis subgroup, meaning ADAS-Cog cutoff of less than or equal to 30, and what the Sponsor refers to as the indicated population. But these were not prespecified analyses or endpoints.

The difference between groups on the CGIC is also small, never exceeding half a point regardless of the time point or population. And this is all within 1/2 point of 4, 4 meaning no change on the CGIC scale.

Although the minimum clinically important difference was not the only or necessarily the primary consideration during review, the primary reason the MCID was considered was that the device did not meet its primary efficacy endpoint of change from baseline ADAS-

Cog at 7 weeks. In order to make a determination as to whether the observed results in the pivotal study represent a clinically meaningful benefit, we looked to multiple sources for information on the MCID. Based on the sources we have listed on the slide, part of our consideration included an MCID range of 2-5 points.

So I want to give you an example. When we take that lowest MCID range that we were given from those varying sources, including literature review, we look at two points. In the example, if you do ADAS-Cog section testing word recall, the patient is given three trials to learn a list of high-frequency, high-imagery nouns. All 10 words are printed on white cards. The score for this section is the mean number of words not recalled on three trials with a maximum score of 10.

A mean change of remembering two additional words, mean change of remembering two additional words on this section, results in a 2-point improvement on the overall ADAS-Cog score. When taking a mean change of 1 to 2 points on the overall score for a single patient over time, the clinical change in the patient may not be exhibited in their overall or global function. As with other standard neuropsychological or neurocognitive testing, there can be issues related to introducing external variables that also affect the results.

Now, I said we considered it, so looking at MCID in context of that range, and the clinical meaning of changes, and the magnitude of the ADAS-Cog scale, here's the pivotal study data in the context of this 2 to 5 point range. Best change in baseline ADAS-Cog at 12 weeks in the post hoc subgroup, which is also on there, is 1.61.

Another way to look at this is to view the ADAS-Cog in relation to the range of the proposed MCID for ADAS-Cog, this time using 2 to 3 point improvement. This is not a prescribed MCID range. We understand there's controversy regarding MCID for ADAS-Cog in the clinical community. This was a range used for consideration of possible benefit, also reasonable assurance of benefit. It is for illustrated purposes on these slides.

Here we review the relationship of the studies and post hoc analyses subgroup at 7, which is indicated in black, and 12, which is diagonal pattern, black and white, and the mean change overall, ADAS-Cog from baseline.

We take this opportunity to address the comparison of the ADAS-Cog magnitude between the neuroAD and approved drugs. The Sponsor promotes this comparison between the neuroAD and approved drugs with respect to determining an MCID in the ADAS-Cog scale that may be lower than 2 points.

To clarify, there is no legal or regulatory requirement that a device meet or exceed regulatory standards applied to FDA's evaluation of drugs. As such, there is no need for the neuroAD to meet the Center for Drug Evaluation recommendations that are listed here. However, we do note elements in the drug regulatory approval process and landscape that bring lower uncertainty to the clinical data, such as statistically significant differences between drug and placebo on co-primary cognitive and functional endpoints. In this case, looking at devices, it would be the device and sham. Results are replicated in at least two adequate and well-controlled trials with large sample sizes.

If the magnitude of change in the primary endpoints are being compared between what is on the drug studies, and remember, in the drug studies, they were not approved based on their ADAS-Cog change, they should be compared along with aspects of the entire methodology and process these pharmaceuticals were subject to in order to gain approval.

I'm just going to mention some other variables, including serial testing and practice effects. Practice effects are when the patient is exposed to a test, especially in short time periods over time, multiple times, and it does not necessarily indicate a true change in their individual ability. Test-retest reliability is the degree to which test scores remain unchanged when measuring a stable individual characteristic on different occasions.

Test-retest reliability in the literature is shown to be 0.9 to 0.93 for the ADAS-Cog.

Depending on the standard deviation, this could correspond to 1 to 3 points, as was pointed out in the previous section, and measurement error of the score at any administration. The Sponsor's representative, in a meeting, when asked about the coefficient of variance, or variables in the ADAS-Cog score, stated that the test-retest is about 3 to 4 points for a site that is not well trained and about 1½ to 2 points for a site that is well trained.

To conclude our discussion of benefit, we have too much uncertainty in the clinical data that we have in front of us for the intended use population. In the dataset where we have the highest certainty, the sham outperform the active. Where we have concerns in the post hoc subgroup analysis and consider it hypothesis testing, the subgroup or the assessment time point of 12 weeks was not confirmed in other datasets.

When focusing on whether the magnitude of change that was seen at this post hoc analysis is clinically meaningful, it does not appear to be consistent or reach the lowest MCID considered -- and notice, remember I said it's not prescriptive -- of 2 points.

Finally, we have concerns with using the ADAS-Cog to screen potential patients because of the measurement error associated and because the less than 30 population seems to worsen absolutely when using the neuroAD device.

We will discuss, in general, risk amongst the device and the procedure. When we're characterizing or discussing risk of a device in a population, there is identified risks of the device in general, and there are identified inherent risks of the population. Both should be considered. In this case, they identified possible risks of TMS and of the population of those patients with Alzheimer's dementia.

That discussion includes risk mitigation measures, as well as does the device have a potential interaction with a risk in the population. As you see here, general risk for TMS is on the left. Alzheimer's dementia, in addition to the cardinal signs for dementia, are on the right. In this case, these two considerations come together when evaluating the risk profile

of the neuroAD.

When we look at the pivotal study, the full cohort of the U.S. pivotal study and their safety population, all adverse events related to the study device were reported as resolved and mild in nature. For a complete list, we note the Sponsor did report descriptions of AEs that occurred in some of the supplemental studies; however, we did not have full raw data for adverse events from several of the studies, and we did not have a complete and detailed way they were reported.

In order to characterize the potential risks of the device, as reported in the supplemental studies, the potentially related AEs listed are here for the patient.

Going back to a few slides, talking about how CDRH assesses benefit-risk, FDA does not believe the benefits to the device are sufficiently characterized, and as such cannot conclude that there is a clinically meaningful benefit in the proposed indicated population. It is not clear why we should conclude that the 7-week results in the pivotal study do not provide a good estimate of the treatment effect. The ancillary analyses and supplemental studies present conflicting results and are difficult to interpret.

Though this would typically end the benefit-risk discussion as shown in the earlier slide, we continue to provide the full assessment of probable risk as well. As we discussed before, we do not have the full safety data for the supplemental investigations. If the safety data is incomplete for a dataset, one of two things could occur. Either the assessor assumes what the safety data results are or should be, or does not use the dataset because it is incomplete and has decreased reliability.

In this case, if we focus on the knowledge of TMS in general, the results of the pivotal study data, and the anecdotal reports from the supplemental studies, we can conclude that the neuroAD is likely a moderate risk device.

FDA is committed to bringing therapies to the market that demonstrate a reasonable

assurance of safety and effectiveness. In the case of the neuroAD device, however, we do not believe that bar has been met. In plain language, the regulatory definitions of a reasonable assurance of safety and effectiveness state that the evidence must show that when using the device properly, the probable benefits to health outweigh the probable risks, and there is an absence of unreasonable risk, or risk to safety, and that there are clinically significant results in a significant portion of the target population relating to effectiveness.

Because of the importance of this patient population and our desire to bring novel treatments to patients, and because we are committed to an open and transparent process, we are seeking panel input on the assessment of benefits and the reasonable, its reasonable assurance, and risks of this device.

Thank you.

DR. JENSEN: I'd like to thank the FDA speakers for their presentation. Does anyone on the Panel have a brief clarifying question for the FDA?

So Dr. Jain.

DR. JAIN: Thank you. Could we have Slide 33 again of the FDA's presentation? This is the waterfall plot slide, which I apologize, I like looking at these things because I'm kind of a geek. But I really appreciate this slide because it shows the individual subject data. And it's really quite concerning for me. The left side of the slide shows therapeutic worsening.

Oh, you passed it. There it is. There it is.

So the left side shows the left -- or I should say, the bars moving in a positive direction show therapeutic worsening. And the most consistent part of this slide that I see is that within the active group, there is a sizable left-sided tail in those subjects who have an ADAS-Cog > 30 that grows between week 7 and week 12, whereas there's no consistent pattern within week 7 and week 12 within the sham. And so if -- there's a bit of an

inconsistent reasoning being applied, I feel, regarding how we're looking at this worsening in adverse effects and how we're looking at benefits of the intervention.

If you -- I've been staring at this for a long time. If you actually look at a cutoff of ADAS of a 5-point change, there are five subjects at week 12 within the active group who are above that cutoff, versus zero in the sham. You know, five out of seven or five out of eight at that time point within that subgroup is a really highly statistically significant result.

And the way that these things get applied in clinical practice is that, you know, if it works in the more mild group, let's try it out in the more severe group. So I'm wondering what FDA's thoughts are in terms of considering cognitive worsening as an adverse effect within a trial such as this, because it hasn't been in any of the further characterization types of slides as anything that's needed.

And then also whether if this is the only data that we're going to see because all of the further trials are going to be on people with an ADAS of less than 30. You know, does it require an additional set of labeling regarding what has been observed within this trial for participants over that age? And also, it would be really nice to see this kind of waterfall plot with a CGIC, not just with the ADAS.

DR. BROOKS: The first part of your question, yes, that was considered and that was part of some of the concerns. And I think, in some of what Laura -- I mean sorry, Dr. Thompson discussed, she tried to elucidate some of that. And I tried to point it out saying that that was a concern because we did not know whether, are we actually having a delayed treatment effect, or a delay because we're getting better, or it was all uncertain?

Okay. This is the evidence we have. This is the evidence we had to review. This is the evidence we had to consider. So as far as additional evidence, that would not be coming from us, at this point, unless Carlos wants to interject in there. I see him.

DR. PENA: On the second part, you know, we may need some time to get the other

request about the CGI information, if that's still going to be needed. But -- yeah. This is sort of the data that was provided. And we are also aware of the trends that occur between this study and other studies where there are different trends happening. So it does create some uncertainty.

DR. JENSEN: All right, thank you.

Okay, so Dr. Dorsey, Dr. Pilitsis, and then Dr. Lyden.

DR. DORSEY: I question -- my understanding is that the neuroAD device has been approved or cleared in other countries. Is that true? Two, have they been cleared or approved for Alzheimer's disease? And if so, what was the basis for that approval or clearance?

DR. PENA: So I think the Sponsor should address that question.

MR. BAROR: Yes. The system is approved in those territories that we discussed for the treatment of mild to moderate Alzheimer. It was approved based on the data that was available at the time of the approval. Notwithstanding, we are continuously providing the relevant regulatory authorities with clinical data as it emerges. I think most importantly, the recent approval that was awarded in Australia was inclusive of all the clinical data that we have shown in our presentation, including the U.S. pivotal data.

DR. DORSEY: Thank you.

DR. JENSEN: Dr. Pilitsis.

DR. PILITSIS: This is a question for Dr. Thompson.

In terms of the CGI data, you know, I think we went through the ADAS-Cog considerably, and I was wondering if you could run us through some of the CGI data similarly.

DR. THOMPSON: So regarding the results, the mean comparison that were presented by Dr. Brooks, you know, my opinion is that it didn't show much of anything. The

point estimates were very small, you know, confidence intervals well include zero. And, of course, p-values were very high. This was both in the full dataset as well as the subgroup.

Looking at CGI, categorically, I'm not sure if the Sponsor presented this, but it may be in the Panel pack where they show the worsening comparisons of patients who were greater than 4 versus less than 4. And they may have shown a post hoc p-value that was less than 0.05. You know, that was after the fact, that responder analysis was not, you know, prespecified, and what it means clinically is not a judgment that I would make. So.

DR. JENSEN: Okay. So we're going to go with Dr. Lyden and Dr. Goodman.

DR. LYDEN: Two quick questions. Following up here on the waterfall plot, Dr. Thompson, and then also your assessment of the qualitative interaction between baseline and treatment group.

As you said, qualitative interaction is really unusual. And doesn't that mean, actually, that that baseline variable can't actually be used in understanding the treatment effect? Because the treatment behaves very differently under that condition.

DR. THOMPSON: So, and this kind of an answer to one of the previous panelist's question on whether we need to think about a worsening -- you know, whether this treatment actually harms. So I was hoping that one of the points of my presentation was that, you know, both of those are subgroups and, you know, if we're going to believe the good one, that's favorable, then we also need to look at the bad one. You know, personally I don't think either one is that convincing, reliable. So, you know, whether or not it's going to be used to make those kinds of considerations is something that would, you know, be done clinically.

But I don't -- you know, this is all kind of after the fact. I think a prespecified interaction test is fine. It looked like there was some sort of evidence of something there. But, you know, dividing subjects into categories after the fact, you know, if you're going to

pick one side, then you'd have to pick the other side. But both of them leave a lot of uncertainty that should be examined with other data.

DR. LYDEN: Well, my question isn't that.

DR. THOMPSON: Okay.

DR. LYDEN: It's actually pretreatment. The protocol hypothesized that the baseline ADAS-Cog would be relevant to the final outcome.

DR. THOMPSON: Right, right.

DR. LYDEN: And then, and what really happened was it behaved differently in the two groups. And they're imbalanced actually. The groups are imbalanced with respect also to the number of 30s. So doesn't that mean you have to stop? You really can't get past that and look at anything else with respect to that variable.

DR. THOMPSON: I guess I'm not quite under -- so imbalanced meaning yes, one of them, one of the groups had a much lower sample size than the other.

DR. LYDEN: Right.

DR. THOMPSON: Yeah. I mean, I think that means that we just don't have enough information there, but what it seems to show is that there could be some harm.

DR. LYDEN: Second question was, you challenged the exchangeability of the various trials in other countries, but is FDA aware of any evidence that TMS biologically interacts differently across countries?

DR. THOMPSON: I don't think I can answer that question.

DR. BROOKS: So just to sort of clarify the other country part, and then I'll go directly to answer your question. The reason we bring up other questions and where the data comes from is also, things are different in other countries in how medicine sometimes is practiced, cultural, things like that. However, as a biological difference, we aren't aware of such, and I did not mean to imply such, if that's what you got.

The Sponsor did, at some point -- and it may be in your panel pack -- state, and it was stated that the motor threshold in the Korea studies seemed to be different than those in the U.S. pivotal, and the intensity given in the Korea studies versus the U.S. pivotal. But I don't have, other than that, any actual biological difference for that.

DR. PENA: And just to follow up on the, you know, other than the threshold data that you are looking at, we don't have any specific datasets that we can refer to. The other thing that we sort of look closely at is assessment tools, and whether those assessment tools are comparably provided to patients in different countries based upon the translation.

DR. LYDEN: Well, okay. So if it's not biological, is FDA aware of any evidence that the assessment tools work differently in different countries?

DR. PENA: Yeah. We don't have any specific evidence.

DR. JENSEN: So Dr. Goodman, and then we'll go over here, Dr. Anderson and Dr. Ellenberg, and then down to Mr. Wreh.

DR. GOODMAN: Dr. Goodman speaking.

I want to repeat a question I asked of the Sponsor, and I think it was responded to by one of the representatives or consultants for the Sponsor, and this goes to back to the cognitive training. I asked whether there was some assessment of performance on the cognitive training, either in terms of tracking errors or response time. And if I heard the answer correctly, I think I was told that yes, that there was tracking of performance, and in fact it was subjects in the active group actually did better than the sham group. And if that, if I heard that correctly, I'm having trouble reconciling that with the fact that the scores on the ADAS-Cog were actually worse in the group that apparently did better in performing a learning task. I wonder if the FDA took a close look at those data and can just clarify that for me.

DR. KEEGAN: I think I have a short answer. We did not receive specific data on the

increasing or decreasing of the cognitive training. So, unfortunately, that is something I think we would request Neuronix to answer.

DR. JENSEN: So the Sponsor can, if they have that information, after the lunch break, discuss that in their session. So let's go on with Dr. Anderson.

DR. ANDERSON: So getting back to the issue of differences, culturally or across countries, did the FDA find any evidence that patients in the Korea studies were not on cholinesterase inhibitors, for example, at the same rate as in the pivotal study the Sponsor presented, since such a high number of patients were on concomitant meds for Alzheimer's disease in the study?

DR. KEEGAN: I think, again, we have to defer to the Sponsor on the Korea studies.

DR. JENSEN: So we'll ask the Sponsor to have that information available after lunch.

Dr. Ellenberg.

DR. ELLENBERG: Yes. Going back to the design of the pivotal study, the Sponsor expected to find a difference of, improvement of -4.6 in the active treatment and a zero improvement in the placebo. And they used standard deviations of whatever they used, whatever they -- oh, it was 4.0 for both groups. That resulted in a 90% power. And that large difference meant that the sample size was rather modest, to run this study.

So with that as background, my question is, when the FDA is looking at this, are you able to look at expected differences that might contradict the sample size computation, in terms of evaluating ultimately the difference of 1.61 in favor of the treatment? I just can't get my hands around the construct of designing a study, looking for a difference as large as 4.6, and then arguing that 1.61 is a minimal clinical difference.

So is there information available on your side, because I did a pretty wide literature search to look at placebo arms of various clinical trials using the ADAS-Cog, in order to get a feeling for what was not necessarily a clinically defined minimal difference, but what's going

on here? What is the variability of the different scores in a non-treated group? And it really varied tremendously.

So my fundamental question is, is 1.61 important clinically? I don't understand that, if it is. And going back to the evidence of what was used in the design, I'm not sure that the Sponsor expected that. Yet now we're being asked to comment on whether or not this is an important result.

DR. THOMPSON: So thanks for your question. I'm not going to comment on whether it's clinically meaningful. I didn't evaluate the study design, but from my understanding of reviewers who did, that difference was not considered to be necessarily, you know, overly large. I think what was -- it was based -- the reason why they didn't think that was because it's my understanding that they had results from the Korea pilot study also to look at, and that was, you know, considered to be, you know, maybe okay.

How many subjects you would need to find the -1.6, I'm sure I've done that calculation, but I don't have it. But remember, that's not really the result in the pivotal study. The result in the pivotal study at 12 weeks was -0.42. So, I mean, you'd need a pretty large number of subjects for that, so --

DR. JENSEN: So I think Dr. -- got your question answered? Okay.

So, Mr. Wreh, you had a question.

MR. WREH: Thank you.

From what it sounds like, from the FDA presentation, it sounds like FDA is focusing on the Korea number 2 pivotal study. I believe Dr. Brooks is recommending the Sponsor, I believe there was second study with a similar subgroup for Korea number 2 study.

My question to FDA is if this product, we are trying to get this product cleared or approved in the U.S., and I believe the patient population profile for Korea and the U.S., I believe -- I'm not an expert, I'm not a doctor, but I think it's different. Why is FDA focusing

on, you know, Korea number 2 study? You know, the Sponsor, they perform a lot of studies, you know, but it sounds like FDA concern is on Korea number 2 pivotal study.

Thank you.

DR. BROOKS: Okay. I can answer that. And maybe it didn't come out clearly because that was one of the things that I was saying, that based on -- we were going to discuss some studies, and some supplemental information that was provided by the Sponsor, that they were going to discuss, and that this was not necessarily what we would have discussed in general, but we have to discuss that as well as the totality of the evidence.

We are not focused on the Korea 2 study. We actually are focused on the U.S. pivotal study, the full cohort. I'm just looking to make sure I didn't say anything I wasn't supposed to. And so that would not -- so if you got that impression, that's not it. I was trying to discuss the evidence that was provided to us regarding the U.S. pivotal, regarding the U.S. pivotal post hoc subgroup analyses, regarding the Korea, the Korea 2, and their post hoc analyses, as well as the supplemental information and studies and clinical observations that were provided to us, because we review the totality of the evidence that's provided to us. However, that was not -- some of it is not necessarily the focus, and some of it did not necessarily lend to the arguments that were made or the contentions that were made by the Sponsor.

DR. JENSEN: I think, Dr. Pena, you have a comment?

DR. PENA: No.

DR. JENSEN: Are there any other questions from the Panel?

DR. JAROW: My name is Jonathan Jarow. I'm the Chief Medical Officer for the Office of Device Evaluation at CDRH, and I just want to make sure the Panel does not leave, or the audience, with any misconceptions. So, number one, the general policy is we accept

outside of U.S. data studies. We then look at those to see if there's problems with generalizability to the U.S. population. And I think you touched on a lot of the factors. It's very rarely a biological difference. It may be concomitant therapies. It may be the stage at which the disease is diagnosed in a different geographic region. But as a general rule, we accept outside U.S. data.

And then the second thing I wanted to clear up, other jurisdictions have different regulatory schema in how they manage medical devices. And so I can't speak for all the jurisdictions that were mentioned, but for instance, Europe does CE marking, and that's based almost purely on safety and not on efficacy. So it's just something to keep in mind.

DR. PENA: And just actually one comment now, then. The additional comment is that we did focus on the pivotal study results. But for completeness, and because the Sponsor has recognized these additional studies, including the Korean study as a validation, we wanted to make sure that the Panel had all of the knowledge that we had, for it to use in this decision process.

DR. JENSEN: Question? Yes. Karen -- Dr. Johnston and then Dr. Proschan.

DR. JOHNSTON: So can I just clarify with the FDA? Because when I read the materials, my understanding was that for both the two Korea studies and the Italian studies, that no adverse events whatsoever were reported. And then what I heard today sounded more like we, the FDA might not have all the information about adverse events. So could you clarify that for me, whether the FDA feels like they have all the adverse events for the Korea studies and the Italian study, or if they do not?

DR. BROOKS: I'm trying to remember what I had written down. I'm getting ready to clarify it for you. I'm just making sure I say it correctly.

The clinical study report states that some of the AEs that persisted, okay, and so, and how they were treated. But then they could not account for primary difference between

AEs that we got in the raw data and that were on theirs.

There was also questions, when we got the raw data, that some of it wasn't -- on what we had, we did not receive it, for certain portions of the study or certain portions of the patients. So that's when we're talking about not having all of the safety data, we're talking about, we don't have the raw data to look at, ourselves. And that was during the review process as well as some of getting ready for this panel.

We usually try to look at the raw data, if possible. And when we don't have that, then we sort of wonder. We also don't have the statistical analysis plans as well as how the safety data was reported for some of the studies. So we have to go by sometimes the paper or the literature, but that's not -- if you know that sometimes those aren't -- what's written in the paper is not exactly what happened during the whole study and having the whole dataset.

Did I answer your question?

DR. JOHNSTON: Yeah, thank you.

DR. BROOKS: Okay.

DR. JENSEN: So just to be clear, you did not have the raw data for adverse events in the U.S. pivotal trial?

DR. BROOKS: No. We did for the U.S. pivotal.

DR. JENSEN: Perfect.

DR. BROOKS: We had all of it for the U.S. pivotal.

DR. JENSEN: Great.

Dr. Proschan.

DR. PROSCHAN: Okay. So I had a question for the FDA, but I also had a question from this morning, so --

DR. JENSEN: The question from this morning will go this afternoon.

DR. PROSCHAN: Okay.

DR. JENSEN: Let's finish up the FDA questions.

DR. PROSCHAN: Okay. I was just wondering, was there ever an analysis done, stratified by, you know, there was this little problem with not everyone getting the proper cognitive training. And so they switched to a 2 to 1 randomization after that to sort of, you know, make up for that. And I'm wondering, did anyone do an analysis which, you know, stratified by when it was 1 to 1 and when it was 2 to 1 and then combining? Because to me, that's really the legitimate way to analyze the results, is by a stratified analysis rather than just saying, I'm going to put everyone together.

DR. THOMPSON: I did not do such a stratified analysis. I actually don't recall how many subjects fell into the 2 to 1 versus the 1 to 1, but I don't believe it was that many. The randomization was stratified by MMSE. That was one, which is a measure of Alzheimer's disease severity, just like ADAS-Cog is. But regarding the 2 to 1 or 1 to 1, I did not do it. Are you referring to the software error that happened?

DR. PROSCHAN: Yeah. I mean, I think that that's what motivated the 2 to 1, the switch to the 2 to 1. But I'm, you know, I --

DR. THOMPSON: I think it was the other way. It was 2 to 1 and then it -- I think, but I may be misstating because this was all before my time.

DR. PROSCHAN: Yeah. Whichever way it went, I'm worried that if there's a temporal trend, you know, there could be --

DR. THOMPSON: Yeah.

DR. PROSCHAN: --- a problem with just putting it all together.

DR. THOMPSON: Since I don't have, in the dataset given to me, who fell under which of those categories, I mean, I would have to defer to the Sponsor to provide the analysis, so.

DR. JENSEN: So if the Sponsor has that information, they can provide that after the

lunch break.

All right. So it's now 12:15, and we're going to break for lunch. We'd like to give everybody an hour for lunch, so we're going to reconvene at 1:15. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any members of the audience. Please take any personal belongings with you at this time. The room will be secured by FDA staff during the lunch break, and you'll not be allowed back in the room until we reconvene.

And for the Panel members, if you have transportation needs that have not been met, please see the front desk, and thank you very much.

(Whereupon, at 11:30 a.m., a lunch recess was taken.)

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

(1:15 p.m.)

DR. JENSEN: Okay. It's now 1:15. I'd like to resume this panel meeting. We will proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Ms. Asefa will read the Open Public Hearing disclosure process statement.

MS. ASEFA: Both the Food and Drug Administration and the public believe in a transparent process for information gathering, decision making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of 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 any financial relationships. However, if you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Finally, if a speaker is reading for someone else, please state this at the beginning of your statement as well.

FDA has received 10 requests to speak prior to the final date published in the Federal Register. Each request will be given 5 minutes.

DR. JENSEN: Thank you.

So in the interest of keeping on time, please keep to your 5 minutes. If I interrupt you and ask you to wrap up, I'm sorry. I'm not trying to be rude, but we do need to stay on

time.

So the first speaker is Mr. Kevin Jameson. Please come forward to the microphone. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

MR. JAMESON: Thank you, and good afternoon. My name is Kevin Jameson.

Dear FDA representatives and distinguished panelists, full disclosure, I do not hold any equity interest in the company, Sponsor. I have no financial interest in the outcome of this meeting, and moreover, the Sponsor has not provided me or my organization any travel reimbursement or any form of compensation whatsoever.

We are not here to endorse. We are here to encourage. As you'll notice, I lead the Dementia Society of America. You can see our logo in front of you. And the reason why I'm here, I'll share with you very briefly.

Approximately 10 to 15 years ago, my wife was in the throes of dementia. She passed away a little over 4 years ago, almost 5 years now. I learned how to be a caregiver. I learned how to hold my tongue when she wanted to go home, and we were already home. I know the pain and the emotional distress that forms of dementia can cause. But I also know that dementia can cause hope and happiness and love and continued love.

And so I would encourage you, and I'm encouraging all the Panelists and the entire FDA to continue this effort. Despite whatever happens to this meeting and the Sponsor, I would simply say continue the effort to make a difference in people's lives.

I'd like to, if I may, in my closing couple of moments, talk about the logo for the Dementia Society. You can see, it almost looks like two halves of a brain, two hemispheres. There are two colors of purple. That's to show you that dementia is not monolithic. There's variety, there's spectrum to dementia. It's not all Alzheimer's. There's Lewy body, vascular, Creutzfeldt-Jakob, frontotemporal, CTE, we all know.

But what I would encourage you to do is also look at the fact that there is separation. That S kind of separates. It can separate the person from themselves. It can separate them from their loved ones. But the real power in our logo is the S, because if you look at how the S is, there's that curve. So think about when your dad or you mom took you out that first time to learn how to drive, and dad or mom said, step on the gas as you're going around that bend. Don't step on the brake. You need to get around that curve.

And so I would say to you that a bend in the road is not the end of the road, unless you fail to negotiate the turn. And as a caregiver, and as somebody living with dementia, negotiating the turns and living a full life is vitally important.

When my wife was diagnosed with dementia, the first thing she said, coming out of the doctor's appointment, University of Pennsylvania, where are we going for lunch? Because she knew she wasn't looking backwards. She was looking forwards. And I immediately booked us a trip to China. We went to India. We went to Egypt. We went to Scandinavia, the U.K. We lived a full life up until the day she died. And I can tell you there's power in things that are non-medical as well, music, the arts, movement, touch. So I would encourage you, that if there's no immediate answer in the medical world, there are current answers in today's world.

And with that, I would like to say thank you for allowing me to speak. Connect with us at any time, 1-800-DEMENTIA, or find us online. Thank you very, very much.

DR. JENSEN: Thank you very much for coming.

So next up is Dr. David Feifel.

DR. FEIFEL: Hi. Thank you very much for the opportunity to speak before you.

Aside from travel, compensation for my travel today, I have no financial relationship with the Sponsor.

By way of background -- and I want to apologize in advance probably for the

hyperverbal speech that I'll be demonstrating because I am very enthusiastic about this field, and I have, want to say a lot, probably more than I'll be able to.

But by way of background, I am a board-certified psychiatrist, and I'm also certified in the subspecialty of behavioral neurology and neuropsychiatry. I have a Ph.D. in neurobiology from the University of Toronto, and I am Professor Emeritus at Psychiatry at UC San Diego, and a research health scientist at San Diego VA Health System. I run a medical -- I'm a medical director of a private neuropsychiatry center in San Diego that specializes in TMS and other advanced treatments for neuropsychiatric disorder.

About 10 years ago, I embraced neuromodulation and especially TMS in my research and also in my clinical practice, believing it is a revolutionary paradigm shift in treating neuropsychiatric disorders that will help us overcome the glass ceiling we have experienced with the traditional pharmacologic approaches to these disorders. In 2009 while at UCSD, I established the first TMS clinical program there. And among other things, I'm a member of the Clinical TMS Society Board of Directors. And I co-chair that organization's Clinical Standards Committee with my colleague, Daniel Press, a Harvard faculty neurologist.

I'm here to speak to you today, as someone with extensive experience with the evolution of TMS for major depressive disorder, since it was FDA cleared for that indication in 2008. And the impact TMS has had on the treatment of, as we call it, MDD, I believe this experience is highly relevant to consider in your deliberation of the application before you.

In 2008 the FDA cleared the first rTMS device for patients with MDD who failed to benefit from conventional antidepressants. That's a large population of depressed patients that we refer to as having treatment-resistant depression, or TRD.

In the past 10 years since then, TMS has already fundamentally altered the treatment landscape of depression. Prior to TMS, the only option for the many, many patients who did not benefit from multiple trials of antidepressants or psychotherapy was

ECT or shock therapy, which is a complex treatment with heavy side effect burden at best, and long-term cognitive impairment at worst. The escalation from trials of medication and psychotherapy to ECT was an enormous quantum leap that frankly many TRD patients just refused to make because of the fear of the side effect burden. And that left thousands of TRD patients feeling that they are out of options.

The widespread availability of TMS today has changed that frustrating situation, and now TRD patients have a highly tolerable treatment to turn to. And this has allowed thousands of them to experience improvement and remission in their depression. Every day I see patients, every day, who have suffered chronic severe depression and have given up hope of living normal lives, sitting across from me when we conduct their post-TMS treatment debriefing meetings. So many of them are grateful, giddy, they're almost incredulous. They're often accompanied by spouses, parents who are equally as grateful.

The durability of the clinical response is very good without maintenance, and excellent with maintenance. And if they do relapse, we see over 80% efficacy for repeat courses, often usually more than a year or 2 years later, if needed at all. And none of this was known at the time of the first clearance because the pivotal studies were limited to the acute term course.

When I first started, not a single psychiatrist would refer a patient for TMS, and often they discouraged any patients who would bring it up from pursuing this. They would typically denigrate the treatment as not effective or without evidence, and no insurance payer covered it. Currently more than half of the six to eight consultations to TMS I see each week are referred by their psychiatrist. Most who refer are serial referrals because they have seen the benefits of TMS in their patients. Today we have 100% insurance coverage.

I just, I'm going to run out of time, and I just want to say that in the 10 years, there's

been incredible advances in TMS from that first treatment. We've seen new coils, faster treatments, something called deep TMS, Theta Burst. None of that would have been possible had the FDA not cleared that first device in 2008. And what's interesting was the pivotal trial --

DR. JENSEN: Wrap up, please.

DR. FEIFEL: The pivotal trial for that first device failed to meet its endpoint of producing significant benefit compared to sham in the population of patients who were enrolled with one to four trials of antidepressant failure. Instead --

DR. JENSEN: Thank you. Your time's up.

DR. FEIFEL: Thanks very much.

DR. JENSEN: I ask Greg and Julie Huber, please to come to the podium.

MS. HUBER: Good afternoon. Can you hear me? Good afternoon. I'm Julia Huber. This is my husband, Greg.

MR. HUBER: Hello.

MS. HUBER: We do not hold any equity interest in the company, and we have no financial interest in the outcome of the meeting, but we are being reimbursed for our travels here today.

I'm short. Sorry.

We would like to thank you from the bottom of our hearts for allowing us the opportunity to share our story. As I said before, my name is Julia Huber, and this is my husband, Greg, which is the patient with Alzheimer's.

Greg was diagnosed with MCI or moderate cognitive impairment in 2015, at age 55. The memory problems began small but escalated faster than we can be prepared for, and he developed Alzheimer's disease within a year. Greg was a very prominent lawyer in our community. Unfortunately, as the disease progressed, we knew it was time to close the law

firm and focus on his health.

Leaving a job that he was so passionate about and having to retire early was very hard for him. Watching a loved one go through something so detrimental is extremely hard on a family, but as helpless as we felt, we were not willing to give up without a fight. We began consulting the internet for options, like many of us all over the world, and learned of the neuroAD therapy.

This treatment was very appealing because it was not invasive, with minimal side effects and great prospect. The therapy was not available in the United States, but we were not going to let that stop us from a great opportunity. At this point, we had nothing to lose except money, and we were filled with hope for what this treatment may bring.

My husband underwent neuroAD therapy in Israel from October 21st to November 28th, 2018. Greg was treated Sunday through Thursday, every day, 1 hour for 6 weeks. He will have spent the hour doing mental exercises in order to stimulate different parts of the brain at the same time he was getting the treatment.

Little by little, we start to see a small difference in his memories. He remembered the number of the bus we supposed to take for the treatments, the place we ate the day before. Sometimes he remembered what plans we had for the day. Lastly, things that he used to ask me 10 times, he only asked one or two, and that is a lot.

These small victories were accompanied with an increase of his self-esteem. And if any of you have ever care take -- been a caretaker of a loved one with Alzheimer's, you know that these small things made a huge difference for both of us. He began gaining back his confidence, independence, and happiness as his memory improved.

This treatment is noninvasive, does not have any side effects that we experienced. Greg didn't have any side effects, not even a headache. NeuroAD therapy by Neuronix is already approved in other countries, England, Germany, France. People in the United

States deserve the same opportunity.

We were fortunate enough to have the means to travel to another country in order to undergo the treatment; however, we shouldn't be, have to do it. Please approve this therapy so that millions of people who cannot afford this travel or get time off work, like I can, have the same opportunity he had.

Thank you for listening. Now I will pass the microphone to my husband, Greg.

MR. HUBER: Hi. I'm Greg Huber. This not easy for me. After going to Israel, as Julia said, we went through the neuroAD therapy. I could see results almost immediately. I can see the results. I see these results as very beneficial. Over time, things have gotten better. I understand it is not a cure and that it represents a process that is a very meaningful one that gives me back my self-esteem.

Thank you very much. I appreciate your time. And please --

(Applause.)

DR. JENSEN: Thank you for traveling and telling your story.

Dr. Jean-Paul Nguyen.

DR. NGUYEN: Yes. Can you hear me?

DR. JENSEN: Yes, we can.

DR. NGUYEN: So, sorry not to be here with you. Firstly, I would like to say that I do not hold any equity interest in the company and have no financial interest in the outcome of the meeting.

I hope the first slide is on the screen.

Now I would like to present a recent experience in France with the neuroAD procedure, combining transcranial magnetic stimulation and cognitive training in the treatment of Alzheimer disease. Our experience relies on a series of 40 patients, with a mean follow-up of near 3 years.

Next slide, please.

Our treatment modality comprised by the neuroAD protocol consisted of 30 sessions done during 6 weeks of treatment. We plan to repeat this by the protocol every year in case of deterioration of the patient, if the patient deteriorates. In the interval, we propose giving a boost, that is to say, 1 week of treatment. For that, we need to evaluate the patients every 3 months.

Next slide, please.

The following evaluation tests were done every 3 months. But the most important scores to follow are the ADAS-Cog and the Apathy Inventory. In these two scores, the lower score you get, in better -- condition you are.

Next slide, please.

Here is represented the evaluation of the ADAS-Cog score and Apathy score at 1 year for the 40 patients. Just after the procedure, at day 45, these two scores improved dramatically and -- did improve at 1 year, underlining that the neuroAD procedure is efficient in the near term.

Next slide, please.

You can see on this slide the evaluation 8 of our 10 first patients, who were stabilized or improved with a follow-up of 1, 2, or 3 year.

Next slide, please.

This slide details the evaluation of patients well stabilized. Two patients had to stop the treatment after 1 year due to a cancer, one case, and in the other case because of a serial mutation. The two patients having the longest follow-up lost only 3 to 4 points in the other group score, in place of more than 16 points, if we be sure, to the natural evolution of the disease. The patient represented by the orange line need only one basic treatment, whereas the patient represented by the blue line need three boosts to be stabilized. This

underlines the need for clinical evaluation every 3 months.

Next slide, please.

On this slide, you can see the evaluation of two patients improved by the procedure. The patient represented by the gray line regained 2.5 points in the ADAS-Cog score. A boost was just necessary at 6 months, and we plan another basic treatment at 3 years. The patient represented by the brown line improved regularly but unfortunately stopped the treatment at 1 year for psychiatric reason. It is a little bit -- but these two patients, in our opinion, can be considered as cured.

This slide, just to remind that neuroAD is an efficient procedure to stabilize or improve the cognitive impairment encountered in Alzheimer's disease.

DR. JENSEN: So thank you --

DR. NGUYEN: And to --

DR. JENSEN: Dr. Nguyen, can you wrap it up, please?

DR. NGUYEN: Yes. It is an effective treatment to stabilize the evolution of AD. It is noninvasive and safe. One basic neuroAD procedure per year with eventually boost every 3 months. It is necessary to follow a patient every 3 months to adapt the therapeutic strategy.

Thank you for your attention.

DR. JENSEN: Thank you very much for calling in and showing this data.

Our next speaker is Dr. Al Najjar Carpentier.

DR. CARPENTIER: Bonjour. Good afternoon, everyone.

Is there a new slide here?

I am Dr. Al Najjar Carpentier. I am neurologist in France and a neurophysiologist qualified from Paris Descartes University.

I don't have an equity interest in the company. I have no financial interest in the

outcome of this meeting. I'll be reimbursed for my travel to be with you here, and I am glad to be with you here.

As you know, the options for Alzheimer disease is very limited in pharmaceutical options and a lot of side effects. We have a real live observation here. We start with neuroAD system in November 2016. I present my observation in two groups, 13 moderate and 12 mild. I observed the MMSE or evaluation before initial treatment and 3 months after the end of the treatment. And, also, I observed the family assessment of patient immediately after the treatment.

So as you see here, in both groups, we observed improvement, about 3 points in MMSE before the treatment and 3 months after, in all, in the both group. Here, I want only to show you that at the end of the treatment, sometimes the family didn't observe improvement, but I advised that you, we should wait, because the real observation and improvement will be 3, maybe 1, 2, 3 months after the end of the treatment.

Here, I can show you that the results in moderate group was less than the improvement in the mild group. Here, only I want to show you my observation about two patients. I start to treatment for 30 sessions at the beginning. They improved about 3 points in the MMSE score. And 1 year after, I observed a decline, and I did again 10 sessions, and they reimprove again.

So I think, in my observation, neuroAD, it's effective treatment. It's safe. And as early we start with, the outcome will be better. Sometimes the improvement need time. And all the patient, my patient enjoy in this treatment.

Here I want only to show you a video about -- yeah.

(French video played.)

DR. CARPENTIER: Merci beaucoup.

DR. JENSEN: Thank you very much for sharing that.

Next will be Anne Sternlicht.

MS. STERNLICHT: Good afternoon, esteemed Panel and FDA members. My name is Anne Brodsky Sternlicht. I do not hold any equity interest in the company and have no financial interest in the outcome of this meeting, but I am being reimbursed for my travel here today.

As I mentioned, my name is Anne Brodsky Sternlicht. I'm a 55-year-old woman who has watched my maternal grandmother die from complications from Alzheimer's, and my mother being diagnosed with Alzheimer's when she was in her early 70s. I am part of an age and gender cohort that is doubly impacted by Alzheimer's disease. We are caring for a parent who has Alzheimer's disease, and we are at risk for it ourselves.

That's actually the wrong presentation.

This population is growing exponentially in size and in desperation --

There is a disconnect between what I see on the screen in front of me and what's on the board, and I'm wondering if we could get that resolved. This is the correct. That's old. Yeah. Can we stop the clock? Is that possible? Thank you. There we go. Thank you. Thank you so much.

As I said, I'm part of a population that is both taking care of a parent with Alzheimer's, and I'm at risk for it myself. This population is growing exponentially in its size and in its desperation for relief, to slow the fatal progression of Alzheimer's disease.

I will always be grateful to Neuronix and the doctors at Beth Israel Deaconess Medical Center in Boston who gave us the most precious gift in life, the gift of time, time with someone you love. To me, Neuronix equals time.

When we received my mother's diagnosis in 2012, none of us were surprised. If Alzheimer's just took her memory, that would have been bad. But it took everything. It changed my mother from a confident, happy, caring individual into a frightened, disoriented

shadow of her former self.

My comments are based on my firsthand experience when my parents came to live with me in Cambridge, Mass. for 4 weeks, January to February 2015, so I could help mom and dad during her Neuronix treatment in Boston. I remember this time well because my parents left sunny Florida to live with me during, I think, the worst, snowiest winter in Boston's history. That's a picture of someone walking among cars.

Mom had been receiving Neuronix treatment for several years, and we were all amazed how she was restored. My brother, who speaks next, has documented this with photos. When mom came to stay with me on January 10th, 2015, although I had previously witnessed the benefits, I could definitely say that it was time for the next round. Each morning, dad and I comforted and assured her that she was going to be okay, that she was safe. And each night when she came home from treatment, she was exhausted, but we knew that relief was around the corner. We knew neuroAD had worked.

During our month together, I saw her cognitively and physically improve. As an example, each night as I helped my mother get ready for bed, I watched her remember how to brush her own teeth, a skill she had lost prior to Neuronix. The point I'm making is I saw first hand the before and after effect.

I didn't know what to expect when mom and dad arrived on my doorstep that snowy winter, but as it turns out, January to February 2015 was one of the happiest times with my parents. I saw my mom come back from the depth of Alzheimer's. She returned to being a woman with love, confidence, and wisdom. She walked through the house with her back straight again. She could look me in the eye and know I was her daughter. I could ask her advice. We watched silly movies together and laughed together.

I only wish I had taken pictures to capture this time. I didn't realize it would be the last time she could receive Neuronix's life-saving treatment. I wish I had known this would

be mom's last time. It was so awful to watch her decline, knowing there was something that worked and yet we were unable to receive it.

We begged the doctors to continue treatment, but we were told it was no longer available. And I ask you esteemed Panel, why? Why is "No, not yet" the right answer? And to please, please consider that as you're making your decisions.

Neuronix was a true gift. It gave us time with our mom that we thought we had lost forever. As a mother, daughter, and a woman who knows this disease has a genetic component, especially mother to daughter, I'm part of a age and gender cohort that is deeply, doubly effected by this disease.

My friends, colleagues, all the radio and talk show airwaves are filled with individuals just like me, seeking help, seeking hope, seeking time, as we watch a parent succumb to Alzheimer's with nothing to slow the process and knowing that Alzheimer's is waiting for us too. It is just a matter of time.

I'm imploring you to allow other families to experience this miracle, this gift, this chance for hope, this chance for more time. I'm begging you to approve Neuronix now. Time is what we need. Neuronix gave us time.

I'll end with this. That summer, the summer of 2015, August, I believe that without Neuronix, mom and dad would never have been able to come visit me in Martha's Vineyard. We rented a house, and mom took a ferry, walked down a dock, and drove a wooded area. I'll just bring your attention to this picture. See my mom, dad and I? See how straight my mom is sitting? She's looking straight into the camera. That's my mom, and that was from Neuronix.

Thank you.

(Applause.)

DR. JENSEN: Thank you very much.

James Brodsky.

MR. BRODSKY: Hello. My name's Jim Brodsky, and I do not hold any equity interest in the company, and I've no financial interest in the outcome of the meeting. Thank you for having me.

My objective is to chronicle my mother's journey, and the positive effects that we personally witnessed from Neuronix.

That's mom in the middle. There she is, surrounded by her family. Mom -- that was in 2009, before Alzheimer's. Mom loved simple things in life, and that started with family and her dogs and delicious food and spending time outdoors and going on simple walks. It's what we're -- I'm really here to talk about is just the simple things in life.

Next slide, please.

Somewhere around 2010 and 2011, we started noticing that something wasn't right. There was anxiety before going out to dinner, confusion at restaurants. Mom was losing personal items, forgetting to take medication. And this next point is incredibly important to me, and that is she stopped talking on the phone with her children. And we come from a very close family, and that time on the phone with mom was truly, it was -- unfortunately, in hindsight, it was magical at the time, maybe more of just a few moments.

Mom stopped driving. She was fearful of cars, and she had excessive worrying about dog safety. Needless to say, in 2012 she was diagnosed with Alzheimer's.

Next slide, please.

Living with Alzheimer's was very challenging. There was a lot of anger. There was a lot of confusion, but there was truly a lot of compassion. Dad was mom's caregiver, and mom went under rigorous medical treatments. Every patch, every powder, every pill became a part of our lives. Some -- we saw tiny progression of help. Some didn't agree with her. It was very confusing.

Next slide, please.

In 2012 to 2013, symptoms really began to impact her life and our lives. There was escalated confusion. Mom had trouble dressing herself. She fell numerous times, splitting her leg open. It was terrible. She had trouble bathing, disorientation, fear of being alone. And a key part was eating. Mom lost her passion for food, and food is where we actually hid her medications for Alzheimer's. And so it was very confusing, as you're begging someone to eat, and knowing there's medicine in there, and they've lost all interest. So we were desperate, and dad discovered Neuronix.

Next slide, please.

So it was challenging, getting mom to go to Boston every day, and she didn't like it. And these are just some of her comments. She did get a headache, she did. And she didn't like the banging on her head, but the results were immediate. And I've learned so much today, but I guess mom was within what we're talking about.

Next slide, please.

This is really important to me. This is a tiny video of mom reading a card that I wrote to her. She doesn't say my name properly at the end. She calls me John; I'm Jim. But that's okay.

I'd like you just to play this, please, because this could never have happened before Neuronix.

(Video played.)

MR. BRODSKY: So it's these tiny, tiny things that I don't -- the scales and all of that, to me, it doesn't mean anything. To me, it was that mom was reading again, and she was able to connect and be a part of our lives.

Next slide, please.

So the treatments continued, and mom continued to be engaged in simple, normal

activities. These are things that she just -- she could never be standing there. I want to point out the far right. This to me was the miracle. I actually took a picture of my mother talking on the phone. I could not believe it. My mom was on the phone, talking to my sister as I was standing there, and it was a miracle. To us, this is a miracle, being able to talk to your children.

In 2014 I was engaged to be married, and I determined I wanted my mother to walk me down the aisle. And before Neuronix, this could never have happened. She would have been scared, confused, disoriented; she would have fallen. It was the most important goal of my life.

Next slide, please.

And she did just that. She walked me down the aisle, and it was incredible. And she was there.

Next slide, please.

And this slide says it all to me. This is mom, laughing with me and talking as she was going -- as people were coming in and greeting her. And people knew that she was an Alzheimer's patient. And it was just incredible.

Next slide, please.

So in 2015, unfortunately, treatments had stopped.

Next slide, please.

The positive traits, in 2016 we saw them diminish.

Next slide, please.

Neuronix gave us 3 months [sic].

Next slide, please.

And, unfortunately, here's where we are now. Mom is no longer at home. She can no longer share our world. But Neuronix gave us time.

Next slide, please.

So, in conclusion, for us, Neuronix was effective. I hope this presentation was effective. And I truly believe that everyone who has someone with Alzheimer's in their life, catching it early, and getting treated, you'll get 3 more years.

So thank you.

(Applause.)

DR. JENSEN: Thank you very much.

Next is Dr. Stephanie Fox-Rawlings.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings, a neuroscientist.

Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We all agree that there is an unmet need for treatments for patients with Alzheimer's disease. The question is whether this TMS device will help fill that need. As a scientist looking at the data, I have to conclude that the evidence presented today does not demonstrate that it works. The lack of a significant difference between the active treatment and sham treatment have been extensively discussed in the FDA materials. It is only with post hoc analysis that the Sponsor was able to find a significant difference, and even then, it was only at a single time point.

As those of you familiar with statistics know, if you test enough comparisons, you are very likely to find a difference that's statistically significant, but that actually occurred due to chance. Moreover, the Sponsor did not use statistical methods to control for these additional comparisons.

The Sponsor provided additional studies to support a benefit, but these studies

included a small number of patients and/or were open label. For those that were double-blinded and included a sham, it is important to know what sham treatment was used and the effectiveness of the blinding. Frequently, TMS studies with better blinding have smaller differences between treatment and sham.

Even with the meta-analyses in the post hoc groups, the largest improvements on either the ADAS-Cog or the CGIC were still very small and do not appear clinically meaningful. On the ADAS-Cog, the largest mean improvement from baseline was about 2 points, which the FDA pointed out equates to remembering two additional words during the recall portion of the test. But recalling two more or two fewer words can vary on separate dates for very different reasons unrelated to TMS treatment. This is especially true with dementia patients whose cognitive impairment varies day to day. The FDA experts and scientific literature both suggest that this is not clinically meaningful.

The Sponsor notes that drugs for Alzheimer's disease that have been approved with similar levels of improvement on the scale, but those differences were still statistically better than placebo, and they were statistically better than placebo on another scale, on a global scale as well.

Since there doesn't seem to be a large safety risk, should the FDA approve this TMS treatment for dementia even though it might not work? Not if the FDA approval is going to mean anything to doctors and patients. The FDA standard is a likely positive benefit-to-risk ratio, yet there's no evidence for a probable benefit based on these studies.

The FDA doesn't consider cost, but it is relevant. Current TMS treatments often cost at least $300 per session. If this is approved, how many millions or even billions of dollars will be spent on a treatment that doesn't work, or at least that we don't have evidence that it works? Even worse, families that can't afford treatment will feel guilty, not realizing that there is no clear evidence for this treatment.

I want to make you also realize that your decision will have implications for similar devices. If this device is cleared, similar devices can be cleared through the 510(k) pathway based primarily on their similarity to this device, with little or no clinical evidence.

Perhaps most important, if we want to find an effective treatment for Alzheimer's disease, research is needed to scientifically conclude what works and for whom. Perhaps scientists would continue to study TMS for Alzheimer's disease even if this device is on the market, but it will most certainly, most likely be for new protocols, including different frequencies, or types of TMS or different training exercises. If we want to know if this device works as described by the Sponsor, better research results should be required before approval.

TMS may eventually be a useful treatment for Alzheimer's disease, but the conditions necessary to make it effective need to be determined before it is approved. If patients receive a treatment that is not demonstrated to work, it should be in the context of a clinical trial that provides free experimental treatment with appropriate informed consent. It should not be in a clinic where patients and their families are paying thousands of dollars for a treatment that they are told is effective but isn't.

Thank you.

DR. JENSEN: Thank you very much for your comments.

Next is Jed Levine.

MR. LEVINE: Good afternoon. I'm Jed Levine, President and CEO of CaringKind, the heart of Alzheimer's caregiving, formerly known as the Alzheimer's Association New York City Chapter. I don't hold any equity interest in the company and have no financial interest in the outcome of this meeting, but I am being reimbursed for my travel today.

CaringKind is the central address for all things related to Alzheimer's and dementia care in New York City. We provide education, guidance, and support for individuals

diagnosed with the disease, and most importantly, those who care for them. I have over 40 years of experience with this population, having worked for close to 30 years as a staff member at CaringKind and prior to that as a volunteer.

In that time, I co-led the first support group in New York City for persons with early stage dementia, and before that, I ran the first adult day program for persons with Alzheimer's in New York. I have counseled hundreds, if not thousands, of families in navigating the complex and emotionally charged journey that is Alzheimer's today.

In the absence of an effective treatment, the best therapy is good care, and that's what we specialize in at CaringKind. We've learned a lot about caring for and comforting the individual and their caregiver, helping them to adapt to the progressive loss of Alzheimer's. The human toll of Alzheimer's is enormous, both for that individual who's affected and their family caregiver.

Caring for a relative with Alzheimer's is unlike any other caring, caregiving experience. I always say, unless you've lived it, done it day in and day out, you don't know what it's like, how draining, how exhausting, how demanding and challenging it is. And the challenges evolve as the disease progresses from the early stage, where the individual is still interacting in many ways as they did, can socialize and engage, to the middle stage where the confusion, disorientation, anxiety, behavioral and functional disabilities become more pronounced, to the end stage where the individual loses language and the ability to walk, sit up or care for oneself, becoming totally dependent on somebody else for all the activities of daily living.

And the behavioral symptoms, agitatedly asking the same question, combativeness during bathing, and the pain of watching someone decline is just so difficult for that caregiver. Caregiving requires superhuman patience and endless compassion. As Susan Miller, a caregiver for her husband and author of *My Life Rearranged* writes, "I think I'm

going to lose my mind before he loses his." Caregivers are desperate for something to help. She writes about the tears that won't stop, the rage, the frustration, not recognizing who she is anymore nor who her husband has become, and fearing that she cannot do this anymore.

I'm reminded of a caregiver in one of our support groups who told us that she wakes up in the morning hoping that her husband has either died or vanished because she cannot face one more day of caregiving for him. And individuals with the disease, who in the early stage talk about being in a race against time are equally desperate for something to help.

In this bleak landscape, the prospect of a treatment that could delay the progression of the disease or even improve function provides previously unimaginable hope for the thousands of families we serve in New York City and the millions in the U.S. affected by this disease. The potential for improving cognition, behavior, and the ability to more fully function in life, returning that spouse or parent as a partner in a responsibility is a priceless gift and one that I fully believe will provide an element of hope, previously and conspicuously missing from the Alzheimer's picture now.

I asked several caregivers what they thought about using a noninvasive treatment for Alzheimer's, which holds the promise of improving function, even if only for a limited time. One of them, Karen, who has been caring for her husband Jason for 17 years -- think about that, 17 years -- said are you kidding? I would have jumped at the chance and so would have Jason. He's participated in several research studies only to be faced with disappointment after disappointment.

Caregivers and persons with the disease would do almost anything if it held the chance to buy them some time, to remain stable, to remain who they are. The data and anecdotal reports about the neuroAD treatment are impressive and speak to this preservation of quality of life, the simple things, maintaining a higher degree of

independence, engagement, and social connectedness.

So on behalf of the close to 6 million Americans living with Alzheimer's and their 16 million caregivers, I thank you for your careful consideration of this novel and promising treatment. Thank you.

(Applause.)

DR. JENSEN: Thank you very much.

Our last speaker is Dr. Vesna Abdulkarim.

DR. ABDULKARIM: Good afternoon. My name is Vesna Abdulkarim. I am a doctor training to become a psychiatrist, and I also work in mental health research at NeuroCentrix in Melbourne, Australia. I do not hold any equity interest in the company, and I don't have any financial interest in the outcome of this meeting. I'm being reimbursed for traveling here today.

I'm here to share our clinical experience with the neuroAD machine, which as you all heard has been approved as a treatment in Australia since 2017. Eight patients have been treated since May 2018. All those patients had a diagnosis of Alzheimer's confirmed by a PET scan. Age group between 65 and 85, 75% of our patients had been on Aricept, and female to male ratio was 1 to 1. All of our patients met the criteria for treatment with having an ADAS-Cog score up to 30.

The treatment was very safe. None of our patients experienced any adverse events throughout the treatment course or at follow-up visits. Seven of our eight patients showed improvement, and the improvement we noted was in areas like orientation, language skills, increased independence and problem-solving skills, improved attention, and improved immediate and delayed recall, which all resulted in improved self-confidence and social life of the patients.

A short case study of one of our patients, who is male, 73 years old, who had been

diagnosed for about 2 years at the time he was referred for neuroAD treatment at our clinic. On initial assessment, the patient had severe language difficulties and remarkable impairment in immediate and delayed recall. And disorientation was the wife's biggest concern.

After the neuroAD treatment, the patient's orientation and language skills improved, both on assessment and also as reported by his wife. The wife also noted increased independence and improved problem-solving skills. She has provided a statement that's been provided to you, and I'd like, if possible, to read a few bits of it.

"My name is Bev Bannard, and I am a 72 year old married mother of two adult children. My husband Ted and I both retired from full-time work approximately 5 years ago. Our daughter is a social worker, and our son works in the IT industry. We have two cats, Dudley and Audrey.

"My husband is 72 years old and had been diagnosed with Alzheimer's since mid-2016. My daughter and I noticed for probably around 2 years prior some deficits in Ted's word finding, the jumbling of words, his orientation to time and place, and his memory. With my daughter's help, we sought the assistance of a geriatric consultant psychiatrist, and this was the start of our journey because we were offered to participate in trans magnetic stimulation, called the neuroAD Therapy System.

"We made the decision to go ahead with the trial of TMS because, really, we had no alternative as there is no cure, no real treatment, and we had nothing to lose. A few aspects did worry me. How would Ted cope with this treatment? And, also, how our life would need to be managed for 6 weeks, driving every day to and from the clinic, and of course, would there be any benefit to Ted?

"We managed really well. This was because Ted agreed to the treatment and because we had a team of very supportive health professionals around us. In terms of the

outcome, there were two aspects to this. Firstly, Ted sat through cognitive testing before and after the treatment, where he was giving score on both times. There were marked improvement in his scoring after the treatment.

"The other aspect was how I saw him. He was less confused, and he seemed better oriented. For example, rather than asking me constantly, every day what time it was, he was able to orient himself, like a person with a healthy brain would. This enabled me to encourage his independence.

"His daily conversation also improved, so he sounded like the person I knew years ago. It was normal conversation rather than the confused banter which was often made up of stories when he went around and around in circles. Another improvement was the lessening of weird comments which made no sense.

"After the treatment, Ted was able to independently fix the Bluetooth connection in his car and connect his iPad to the TV screen. He was also been able to stay at home whilst my daughter and I traveled overseas for 3 weeks with no problems. His psychiatrist also made mention that after the treatment, he could not pick up anything wrong with Ted if say, for example, he randomly sat next to him at a railway station and sparked up a conversation. The treatment seemed to push the symptoms back. He was more settled, which was a relief to me."

So, overall, the treatment is safe and well-tolerated. None of our patients experienced any side effects. The patients actually enjoyed the experience. They love coming back to the clinic. They get more and more engaged in the cognitive training, which requires less practice time and less explaining after a few sessions. The treatment can be used as an adjunctive to existing drugs, as you all know, and majority of our patients showed improvement, both reported by their family and also on formal cognitive assessment.

Thank you.

(Applause.)

DR. JENSEN: Thank you very much.

Does anybody on the Panel have any questions for any of our Open Public Hearing speakers?

(No response.)

DR. JENSEN: I now pronounce the Open Public Hearing to be officially closed. Thank you very much for the participants.

We will proceed with today's agenda. We will now begin the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

Before we proceed to the Panel deliberations, I would like to ask our non-voting members, Ms. Veverly Edwards, our Consumer Represent; Mr. Elijah Wreh, our Industry Representative; and Mr. James Taylor, our Patient Representative, if they have any additional comments.

Ms. Edwards, do you have any comments?

MS. EDWARDS: Yeah, I do.

So I want to thank all the families that came and presented. And I'm somewhat conflicted because I have a daughter that has a neurological condition that there's no cure for, but at the same time, I have to think of the American public. And to release something that hasn't been fully vetted, or we cannot determine the efficacy of it, I think would be irresponsible on our part, because we can't determine it and it's a high-cost treatment. So you're releasing something to the public who has very little hope right now, right. So we

release this and then they're thinking, oh, wow, yeah. But who can afford it?

So then you may have Americans pulling retirement funds out, you know, pulling funds out of retirement accounts. You have Americans mortgaging homes, you know, because you want this for your loved one. So I think we really have to be responsible and think, you know, what are we going to do to the public if we were to release this information for a condition that there isn't, you know, very little hope for. So that's my comment as a consumer.

DR. JENSEN: Thank you very much for those thoughts.

Let's see, Mr. Taylor, would you like to make some comments?

MR. TAYLOR: Thank you. I'm the Patient Representative, and my chair is very crowded. I represent over 21 million people today, about 6 million people living with Alzheimer's and nearly 16 million care partners, caregivers, some of whom have spoken eloquently today, and their representative has spoken well as well.

My wife, Jeri Taylor was diagnosed about 6 years ago, and she is in the mild stages of the disease, and we are very active in trying to bring a message of hope across the country in speaking engagements. Next week we speak to 600 people in Dallas-Fort Worth, at an Alzheimer's Association event. But I can tell you that there is much gloom and dismay in our community.

The participation rate in Alzheimer's clinical trials is around 2%. And this is a tremendously challenging problem, for curing Alzheimer's, because there are many drugs that need to be tried, trialed. And most every trial is unsuccessful in meeting their objective in enrolling participants on a timely basis. And it's just getting worse because with all the additional research dollars we have, there are more -- there's a greater and greater need for trial participants.

But because of 400 failures, it's hard to encourage people to enroll in clinical trials.

The average life expectancy, once symptoms are visible, is 14 years. Alzheimer's is the sixth leading cause of death in this nation, and of the 10 leading deadly diseases, it's the only one that cannot be cured, prevented, or slowed. PCPs rarely give cognitive exams at the Medicare annual wellness exam because it takes time, and they only have 15 minutes, but also because there's little they can do if they diagnose early dementia. Therefore, early diagnosis is rare for dementia, and therefore recommendations into clinical trials does not often happen at an early stage.

So where are we today in my view? I understand that this is a perplexing problem. I worked for IBM for 30 years. I understand rules and regulations and bureaucratic problems. I know it's difficult. But I've also seen what magnificent things can happen when we work together and think outside the box.

I see a product that's generally accepted as safe, moderately safe, and a product that's being marketed, I think, to nearly 400 people in Europe, Australia, and Israel, and some reportedly very positive results today. And I look at my community, and I see very little hope. My wife, for 4 years, has been in the clinical trial, pharmaceutical trial that has been the greatest hope in the trial community. And this morning, Biogen announced that they were withdrawing aducanumab. I just had to call her and tell her that that was the news. She's doing okay, but it's very hard. It's very hard to go back out next week and recruit people in Texas after we've just had such a difficult failure.

So I'm saying to myself, we've got something that's safe, we've got something that there's a lot of reported success, and yet we haven't met the primary results. I've got to say, I could have slept through most of this morning. I don't understand a lot of the Panels. Thank you, FDA, and thank you, Neuronix, but a lot of this was over my head. But I'm trying to understand if the only choice we have is to send Neuronix back for another 2 years of testing and to deny the American Alzheimer's community the opportunity to have this

treatment.

Is there another way? Is there a way to send them back for further testing and provisionally allow this test to go to market? We don't need to give it the Good Housekeeping seal of approval, but is there some other route? I hate to deny the 6 million people who have Alzheimer's a way to have some hope and to have some treatment. So I just ask you, can we think hard about any other possibility?

Thank you.

DR. JENSEN: Thank you for your comments.

Mr. Wreh?

MR. WREH: Thank you.

Just want to mention a couple of things to my colleagues on the Panel, that this pathway for approval or clearance, as FDA say, is a de novo pathway. The product, when it gets approved or cleared today by the FDA or tomorrow, it'll be considered, you know, a Class II medical device, and it will go through the postmarket process, which is a 510(k).

FDA said the device, they describe it as a non-significant risk product. And if FDA clears this product, it will be used as a predicate device to other medical devices that will come later on. So I know FDA concern is on safety and efficacy, but the product is already approved or cleared in Australia, Israel, and the EU. The product was reviewed by the EU and has received CE mark approval. It is used in Australia, and there is no serious adverse event on this product.

So I think panel members need to take a deeper look at this product, that has been used OUS, is not a new technology. It's been around for some time. So I think they should provide FDA their experience from a clinical perspective, how this product would benefit our patient in the U.S.

Thank you.

DR. JENSEN: Thank you very much for your remarks.

So both the Sponsor and the FDA were responding to the Panel's questions posed this morning, and I don't think there are any leftover questions for FDA, but there were questions for the Sponsor. So if the Sponsor could come to the podium. And the questions that were asked were Dr. Anderson's question about drugs in the Korean study, and I think Dr. Goodman, Dr. Proschan, and I think Dr. Postma all had questions, correct?

So let's start with Dr. Anderson's question.

MR. BAROR: So if it's okay, I think, we made over the break a short presentation. I'm not sure it's in the order that you have just listed, so if it's okay, we run through what we have, and then whatever is left, we will happily address. Okay?

DR. JENSEN: Great idea.

MR. BAROR: So we're now going to answer first the issue of the safety. So we'll present what we have by the company at the completeness of our safety data from all other non-U.S. pivotal study. Then Dr. Sabbagh will show the all adverse events table that was requested, FDA requested, and answer all your safety questions.

And Dr. Pascual-Leone will then answer on the issues of the cognitive progression versus the delayed effects and the mechanism, the medication that was used in Korea. And, finally, for Dr. Lavin, there was a question on the statistical stratification of 1 to 1 and 2 to 1 that he will address.

So, with that, I'll hand over to Moran Ploznik of Neuronix.

MS. PLOZNIK: Hello. So the Panel asked about the completeness of the safety data provided to FDA. All safety data available to Neuronix was provided to FDA. To account for the data that is missing, some of the studies were conducted independently, so the data is not available to Neuronix. We asked for it. We don't have the listings. We asked for it, and we were answered that there were no serious adverse events related to the device.

Please note that we are also obligated to provide safety data in the reports to the European authorities, and we monitor for that. But we don't have the listing, so we provided everything we have. And there are no other safety concerns that were not raised in this meeting.

DR. SABBAGH: So I'm going to first walk us through the adverse events, if you would put those slides up, the first slide.

So people were asking about the frequency and the number of adverse events and how was it impacted. You see, this is the slide 1 of 2 showing the adverse events. You see that the numerical frequency of these events is quite low, per cell. And there was no serious imbalance. In totality --

And I'm going to go to the next slide, please.

This is the rest of the adverse events. Again, numerically, not huge numbers. And this is -- I just want to say that the total number of adverse events was higher, but you could have more than one adverse event per participant, and that's why you had it. So, again, these are all mild. They're very -- you know, and this is a list that shows it.

I don't know if that answers the question. I think that was the question of the frequency. And there was not -- it's not showing that the technology's skewed. I also want to tell you that, of course, as we've been, pointed out in this discussion, you know, this technology or the analogous technology has been administered over a million times for other indications by other companies, with no major treatment adverse, treatment-emergent adverse events, except for, of course, seizures as you heard, and this, our technology does not have it.

Next slide is showing you the SAE rate. Oh, no, there is no SAE. So I just want to point out that there were no seizures, no SAEs, no withdrawals due to adverse events. So we believe that the strong evidence of safety, while the comments of the FDA are valid

regarding theoretical risk, they were not observed in the pivotal or global use, to date.

Next, there was a question about the CGIC. And the question that was in front of us for the CGIC was about harm. So the question that was posed in the morning session was, if you were above 30, and we talked about the waterfall plots, etc., does the patients above 30, and that was posited by the FDA, cause harm? And the answer to the question is, is when you look at the CGIC data on the same group, you see no evidence of harm. I would posit that actually, if anything, it continued to show a neutral effect and that what you saw in terms of cognitive decline was a progression issue, not a safety issue related to the technology.

I hope that answered the question as to whether the technology caused harm in the moderate Alzheimer's dementia cases, because that was implied.

The next was there was a comment about the side-by-side cholinesterase inhibitors versus the neuroAD technology. And we want to comment a couple of things about that. That side-by-side comparison, as was commented by the FDA this morning is correct, but it doesn't factor into the account that the neuroAD technology was not against true placebo. This was against standard of care. So, in fact, the standard was -- actually the threshold was higher in the neuroAD compared to the cholinesterase inhibitors.

Finally, I want to point out that the Panel's consideration of benefits relative to risks, I think it's important to remember that we have 13 sources of data all trending in the same direction, so as to suggest that this is a random finding does not appear to take into account all of the information that we have. I would refer the Panel back to the forest plots we presented on this issue.

I also know that from years of experience in AD studies that a positive finding on a dual endpoint is important and rare. Dr. Schneider stated that the combination of ADAS-Cog and CGIC is important. We'd be happy to discuss these issues further with the Panel.

DR. JENSEN: The Panel members who had questions, first --

DR. GOODMAN: I don't think mine was answered.

DR. JENSEN: First of all, the Panel members that had the questions that were answered, were your concerns answered? Of the Panel members that had asked questions that we asked them to gather the data and show, which they just showed, everybody happy with that?

DR. GOODMAN: My question wasn't answered.

DR. JENSEN: There we go. So now is a question that's not answered.

Dr. Goodman, can you restate your question?

DR. GOODMAN: Yeah. I'm sorry to belabor it, but this has to do -- I had asked the question about the cognitive training. And I believe you said that the performance was assessed, you know, looking at whether it was error rate or time to respond. And I thought I heard you say that it was better in the active group, so I just wanted to see those data.

MR. BAROR: Yeah. It's coming. Absolutely.

DR. GOODMAN: Okay.

MR. BAROR: So, first of all, let me clarify. I may have not been clear and potentially caused some confusion. So two studies, two of the supporting studies, the Harvard one and the Italian study, small studies, had the three arms. The pivotal U.S. study did not have cognitive training during the sham intervention. The subjects were sitting in the same chair. So we cannot compare in the pivotal study the progression in terms of the 6 weeks of training between the two groups because only one group had the cognitive training.

In the two small studies, the Italian and the Harvard study that had three arms, what was found in both of them is that the overall effect was such that those individuals, those participants that were getting real TMS combined with real cognitive training, as compared to those that were getting sham TMS compared with real cognitive training, showed a

steeper learning curve, so they progressed faster across the cognitive training in the adaptive design. As the FDA pointed out, it was a personalized adaptive algorithm, so they eventually, effectively got further into the training when they were primed by real TMS.

What we can look at in the pivotal study, slightly different, what we can look at is that same question of progression in the individuals with the ADAS-Cog ≤ 30, the indicated population, versus those with ADAS-Cog of higher than 30, and that you see here. And so what you see here is that when one contrasts the progression in the 6 weeks of training, between the individuals with a baseline ADAS-Cog of greater than 30, and those with a ADAS-Cog of less than 30, the milder effected progress further along. Again, not particularly surprising.

That was not true for all the tasks. It was particularly not the case specifically for the visual motor tasks that were designed to engage the parietal cortex. That's what you see here, of course, the differences.

Perhaps, in the same context, if I may, just to make one last point, it was discussed a number of times that the TMS treatment and the link to delay effects, and you were asking appropriately about what happened during the TMS cognitive training performance, of course, by design, the 7-week time point and the 12-week time point are both after the, quote, "treatment," are both after the intervention has been completed.

Being after the intervention does not mean that they're after the end of the therapeutic effect of that intervention. By definition really, by design, all TMS indications of therapeutic effects end up banking on an effect that comes after the application of the TMS. If it was necessary to have the effect during the TMS, one would have to be carrying around the TMS device all the time, and that is not the hypothesized mechanism of action of TMS.

The hypothesized mechanism of action is an offline effect after the course of TMS.

And that's not unique to TMS or to this indication. Other neuromodulation interventions show the same thing. Deep brain stimulation, for example, or ECT shows an effect that comes offline of the intervention course.

DR. GOODMAN: I'm satisfied with that response. Thank you.

DR. JENSEN: Do any other --

MR. BAROR: There was another question in regards to the medications that I wanted to address as well, if I may.

And so the specific data you see here, the first question was whether there were differences in the medication between the Korean studies and the U.S. pivotal study. In the Korean studies, all patients were on donepezil. They were overwhelmingly on a relatively small dose of donepezil, and none of them was on an NMDA inhibitor, antagonist. In the U.S. pivotal study, about 2/3 of the patients were on acetylcholinesterase inhibitors, and about half of those patients were in addition on memantine.

And this is a very relevant question to the -- so thank you for asking it, because if you look at the interaction between medication effects and TMS effects, which has been looked at, then there is differential effect. There is a modulator effect of medication, particularly in terms of the speed by which TMS induces excitability changes. And perhaps, because of that, if you look at the data of the U.S. pivotal study, in the patients that were not on any medications, which you see here, an *n* of 12 at 7 weeks and 12 weeks, you see that they show a much greater effect on the ADAS-Cog than those that were on medications, that don't show really, an effect at 7 weeks and it comes at 12 weeks.

I know that that seems a little contradictory to the Korean study, but the results that showed the effect -- but, again, remember that in this case, these patients were on much higher doses of cholinesterase inhibitors and on memantine for the most, half of the cases, whereas in the Korean study, they were on perhaps a suboptimal does of the medication.

And the relationship between the effects of TMS and the pharmacological effect of cholinesterases and memantine has been looked at, and it is dose dependent, so it could have something to do with that.

DR. JENSEN: Thank you very much. Does anybody else on the Panel have a question for the Sponsor?

Yes. Dr. Proschan.

DR. POSTMA: Hi. Dr. Postma.

I'm wondering if you could talk a little bit more about the diagnosis of Alzheimer's disease for these participants. Was there a distinction made between -- I mean, I know you talked about the DSM-IV, but beyond that, were there any other confirmatory tests done? Were there other types of Alzheimer's disease-related dementia participants included, such as FTLDe or vascular dementia?

DR. SABBAGH: So the indication was --

You will put the slide, AD confirmation? Yeah, please.

DR. SABBAGH: So they met DSM-IV criteria. So to be very clear on this, biomarker evidence of amyloid positivity was not included. This, of course, predates the common utility of that. We relied on the clinical diagnosis by expert clinician. The other exclusionary conditions were excluded, Lewy body, Parkinson's, FTLDe, vascular dementia. All of them had had scanning to ensure there was no, nothing like mass and normal pressure hydrocephalus and, you know, hypothyroidism and B-12 deficiency.

So and we had expert clinicians. The 10 site clinicians, PIs, myself being one of them, had many, many years of experience in diagnosing and managing clinical patients who have Alzheimer's dementia. So I feel like the selection of the population did reflect the disease state.

DR. POSTMA: Okay, great. Thank you. And then how were other -- were other

confounders looked at between the sham versus the test group? For example, I'm thinking of depression in particular.

DR. SABBAGH: So I'll let probably you -- Dr. Pascual-Leone. I do want to say to you that major depressive -- in the exclusion criteria, MDD, active MDD was excluded. We did a geriatric depression scale as a screening, and showed that if they were above a certain component, they screen failed. So active depression was screened for and was excluded, but Dr. Pascual-Leone can comment further.

DR. PASCUAL-LEONE: Thank you very much for that question.

We actually did worry a fair amount, I did worry a fair amount, particularly, about the possibility of depression, because as you are aware, TMS can have an antidepressant effect. And so we worried that perhaps some of the effects could be driven by mood effects. To that end, depression was an exclusion criteria for the trial. So at baseline, patients were assessed. That obviously is not enough, is the sole argument, but it was the beginning of it.

The TMS protocol for depression, if you want to have an antidepressant effect, is quite different from the protocol for dementia that you just heard about. There is, in the case of depression, a single region that is stimulated, and the number of stimuli to that region is much greater than the number of stimuli that were targeted in this case.

In addition to that, because of the design of the neuroAD treatment, individuals received stimulation also to the contralateral hemisphere, which in the case of depression would have countered the effect of the stimulation to the left hemisphere. So that, you know, we don't think that it was a mood effect that was being induced. And we did look at it for the concern of the possibility of it.

DR. POSTMA: Okay. But mild depression was not screened for, just major depression?

DR. PASCUAL-LEONE: Major depression was the exclusion. And mild depression was only screened for inasmuch as assessing the response to the stimulation, but was not an exclusion.

DR. POSTMA: Okay. And then, finally, I'm just wondering. You had talked earlier about cognitive training alone in some of the studies. Do you have similar data for TMS alone in this population?

DR. PASCUAL-LEONE: So we didn't present any such data. There's been two systematic reviews of the literature on the use of TMS for cognitive decline and dementia in general, not specifically just alone for Alzheimer's disease, the last one of which was just published in current review of *Neurology*.

There is a number of studies, relatively small studies that have looked at it. Mostly, they have looked at specific domains, the short-term effects with the short courses, and just looking at naming. For example, Cotelli, about a decade ago looked at the effect of naming accuracy, immediately after a single session of stimulation. There were a number of studies from Cotelli on memory, showing the opposite, showing no memory side effects. But there's been no study that really was designed to look at the overall effect of TMS on cognitive functioning in a sustainable kind of way.

Thank you.

DR. JENSEN: Dr. Proschan, I think you had a question.

DR. PROSCHAN: Yeah. Earlier this morning there was a discussion about, you know, whether you're following the statistical analysis plan, and whether some of the p-values might have been, you know, not really prespecified, those analyses. It seems to me that on the CGIC, I think the Sponsor said that there was, it was -- that they reported a chi-square test. I've looked in the statistical analysis plan. Not only is there no chi-square test specified, but it specifically says on page 19, "Comparison of CGIC at week 7 and week 12

between groups will be done by independent group's t-test or Wilcoxon rank-sum test." But I noticed that the chi-square test was statistically significant; the Wilcoxon test was not.

So, you know, what's going on there? Why was that chi-square p-value emphasized? And I would also note that the statistical analysis plan says, "Secondary analyses are considered exploratory, and statistical testing where appropriate will be done without overall control for Type 1 error." So, to me, that says that the reason you're not controlling for Type 1 error is because they should be considered exploratory and by no means definitive.

MR. BAROR: Dr. Lavin, please.

DR. LAVIN: Phil Lavin, I'd like to comment on that.

Basically, it comes down to the pragmatics. If you have the data, it should be properly analyzed. The way I would analyze it would be with a Wilcoxon rank-sum test. That test was statistically significant, very close to it, depending on both populations. The chi-square tests were 0.037 and, you know, let's see, the other one was, you know, 0.041. So those were indeed what was done. And probably in this day and age, I would do a Kruskal-Wallis test on it, to compare to ordinal distributions. That would be the way I would approach it. And you're correct about your observations on page 19 of the SAP plan.

MR. BAROR: If I may, Dr. Alvaro Pascual-Leone will also say a few words on this question.

DR. PASCUAL-LEONE: I just wanted to remind you as well, in regards to the question, that even if exploratory, the other studies that we presented, as you saw from the forest plots, do show a consistency where all the studies essentially showed a positive effect.

DR. PROSCHAN: But you were allowed to pick and choose which studies to show us. Right.

DR. PASCUAL-LEONE: Well, I --

DR. PROSCHAN: For all I know, I mean, you know, I don't know whether you saw other studies and didn't report them. I don't know if that represents the totality of studies. And that's the problem with meta-analysis. You do a meta-analysis after you already know the results of the studies. So if you're allowed to pick which ones to include in the meta-analysis, and you're allowed to include a subgroup that was, you know, showing benefit, you know, in this study, it's not surprising that that would go along with what -- you know, that that would support the conclusions that you're making.

That's why I really don't think you can make anything out of some of the p-values that have been reported today.

DR. PASCUAL-LEONE: I don't mean to debate that with you. I'm simply saying that, what we did in the forest plots was not to actually pick certain studies, but simply put all the studies that have been published together, not trying to clarify which ones were control clinical trials, which were a case series and stipulating in that way. And what we found significant there, or remarkable there, as you can see in the slide 3 -- sorry, number 3, yeah, is the fact that even accounting for the variability of the studies, for the small studies -- this is just not trying to do a meta-analysis, it's simply describing the effects that they describe, that the majority of those studies are to the left of the zero line, and showing an efficacy effect, even though some are small and shouldn't be weighted too much.

DR. PROSCHAN: So do these represent all the studies that have been done?

DR. PASCUAL-LEONE: Yeah.

DR. PROSCHAN: They do? Okay. That's helpful.

DR. JENSEN: Just, Dr. Pilitsis, I think, has a question.

DR. PILITSIS: I had a question about dosing. When I look at page 29 of the Sponsor's submission, there's a comparison between neuroAD and NeuroStar. And the dosing looks different, less so for neuroAD. The fact that there were no seizures suggests that it may be

lower, too. The fact that the motor thresholds appeared to have some impact -- or differences, and may have had some impact on data, indicate that dosing may be different for different patients.

So my question is what do you think the role of patients receiving different doses was on your outcomes?

MR. BAROR: So we did not have a study to test for different dosing. Like you rightfully say, in the Panel pack, we had the comparison of the dosing, of the neuroAD versus the NeuroStar system. And you rightfully point out that it's a lower number of pulses per day, and also it's split among several brain regions to enhance the safety and lower the risk of seizure. But as per your question, no, we haven't had the opportunity as of now to test kind of a multi-response versus different dosing and different parameters and characterization of whether different parameters would yield different outcomes.

DR. PASCUAL-LEONE: If I may just add to it, you're absolutely right, that given the technique of defining the intensity of the stimulation, this was a personalized dose in the sense of absolute intensity of the stimulation because it was based on the individual motor threshold. That is relevant, because as we talked about this morning, the more severely affected patients do have a different motor threshold overall than the less severe and so effectively got less intensity of the stimulation.

The same is true as the FDA correctly pointed out with the cognitive training; it was personalized. That is the design of the intervention, is a personalized intervention.

In regards to the comparison with the NeuroStar, the number of pulses is much less, and the intensity is indeed less. And the reason for that is for two reasons. One is because we were targeting different areas, and the different areas do have different excitability parameters and profiles. And it was driven by a safety decision. It may well be, but it's a hypothetical question, that increasing the intensity ultimately may lead to a higher effect,

but it may be that's what the Korean studies suggest, in the smaller sample that had a higher motor threshold. But it could have increased the risk, and so that was a decision made on the intensity, to fall within the safety guidelines and be able to safely target different locations.

Thank you.

DR. JENSEN: Yes. Go ahead, Dr. Duff.

DR. DUFF: I was wondering if somebody could clarify where the cognitive tasks came from. These aren't necessarily cognitive tasks that I associate with Alzheimer's disease. Similarly, the brain regions that they target aren't necessarily sort of the primary ones that I think about with Alzheimer's disease as degeneration. So maybe just a little clarity of where the task came from and why these brain regions.

MR. BAROR: Yeah. So that's a good question, relatively a little bit all going back to the history of the development. It was done based on the state of the art of the literature that was available from like 10 years ago, relating what cognitive tasks can be associated what cortical regions, bearing in mind that we can only reach so deep into the brain using TMS. Obviously, if we were to go to a different modality with an invasive procedure that can engage deeper brain regions, and so other cognitive tasks, then maybe the outcome would have been different or better.

But, nonetheless, the idea was to identify what cortical regions are close enough to the head to be stimulated by the TMS, and so find the matching cognitive tasks that relate to them. But then it was done based on fMRI, and I think it was the beginning of PET scans. But I have to go through the literature and dig out more details if this is of an interest.

DR. DUFF: So I mean it just feels that maybe these weren't developed specifically for Alzheimer's disease but based on what you had available. I mean, it seems like it's much more -- would be appropriate for, you know, an aphasic patient, that I could see that a

language disturbance, this may benefit those patients more. And, admittedly, patients with Alzheimer's disease do have difficulties with language, but it's not necessarily the primary thing.

MR. BAROR: It was developed in the view of Alzheimer, but I think that regarding the -- overall in the holistic contribution of the different cognitive training to the overall cognitive performance, maybe I would defer that to Dr. Pascual-Leone.

DR. PASCUAL-LEONE: So I think that the reason why specific brain areas were targeted match with specific cognitive tasks is probably many-fold. And one of the components is just a limitation of the TMS. As Dr. Baror was saying, you can't reach to and through single -- to retrosplenial cortex, sorry. You cannot reach to mesial temporal structures. And so with that, there was one layer of limitation of what areas in the convexity it would make sense to reach.

The second was given what we know about the presentation in patients with Alzheimer's disease -- early, what cognitive domains would be worth targeting. And that decision came to visual-spatial sort of orientation and attention, hence the parietal lobes. The tasks that were identified and the location that was identified was informed initially by imaging studies that had shown abnormalities in patients, not just in healthy controls or what areas, but there was a logic for the parietal.

The language networks or the language studies was prompted by the naming difficulties that patients often have, as you know well. That is not simply a lexical axis issue. It's more complex than that. And so whether simply targeting Broca, Wernicke would really lead to a beneficial effect in the naming tasks is debatable, but that was the rationale for that.

And then those other frontal cortices had to do with more executive function, including working memory deficits the patients may show and certainly judgment-related.

So memory specifically was not targeted, and that had to do with the fact that there is a limitation in reaching directly to the mesial temporal structures.

DR. JENSEN: Dr. Baxter.

DR. BAXTER: Yeah. Just maybe one more question while we're talking a little bit about the protocol. When the primary endpoint for U.S. pivotal wasn't met, was it ever considered to change, you know, the treatment regime? Or was that ever taken into -- you know, has it always been the 6 weeks of treatment? And/or was there any discussion of changing that regime? Excuse me.

MR. BAROR: You mean to kind of to prolong the intervention phase?

DR. BAXTER: Well, so when, you know, the -- like I said, when the primary endpoint wasn't met at the 7-week mark, you know, you had obviously come up with the treatment strategy. Was that ever in discussion, as to whether this was the correct dosing, so to speak, and treatment regime for, you know, for showing your benefit?

MR. BAROR: I don't remember that was discussed in thorough. I don't think it was discussed with FDA. But maybe I'll have to discuss this with my colleagues and revert back after the next break on that issue.

DR. JENSEN: Dr. Anderson.

DR. ANDERSON: Aside from the geriatric depression monitoring at study entry, were there other systematic psychiatric monitoring scales administered during the study? I didn't see a Neuropsychiatric Inventory or other psychiatric scales in the protocol.

MR. BAROR: Yes. Dr. Sabbagh, please.

DR. SABBAGH: That's correct. We did not monitor those things after screening for it at base -- at the screen.

DR. ANDERSON: I'm concerned by that, because it seemed like your rate of adverse events, of psychiatric adverse events were low in both the treated group and the placebo

group. So I wonder, was it just that you weren't asking about psychiatric events in a structured way and that's why they weren't recognized? You know, patients come in to a study like this for cognitive treatment, and their caregivers understand it's for memory treatment. They don't necessarily make the connection that something that stimulates for memory treatment could also cause psychiatric side effects.

DR. SABBAGH: So that is true. We did not do a specific NPI or NPI-Q, as you point out, or a BMAI. I do want to talk to you about the fact that the CGIC has certain elements in it that capture neuropsychiatric features, and that was not flagged at any time.

DR. JENSEN: There was a -- I think, Dr. Jain, you asked for a slide from the FDA on the 7-day CGIC. Can we put that slide up? And if you could restate your question or your point.

DR. JAIN: Felipe Jain. So it's a little hard to parse the bars on this slide, but my point in relation to the ADAS-Cog slide was that it seemed that many of the patients were lumped toward the -- in the active condition whose ADAS-Cog was over 30 were lumped on the left side of this. And then the Sponsor showed a slide suggesting that the pattern was not replicated with the CGIC. But from this slide, I really can't parse very well what's --

MR. MARJENIN: So my powers of PowerPoint, they are what they are. At least you got a pretty picture to look at. So my name is Tim Marjenin. I am the Chief of the Neurostimulation Devices Neurology Branch at FDA. I work under Carlos.

So what -- I would have liked to give you a much better representation of these data. The way the timing worked out, the bar chart is the best that I can do, so using a similar convention as with the other waterfall plot. Each individual bar -- and I understand that it's hard to tease out which one represents an individual patient, but each one of those represents one individual study subject, both in the active group and the sham group at 7 weeks. The filled bars are those subjects who have a baseline ADAS-Cog that's less than or

equal to 30. The empty bars are those study subjects who had a baseline ADAS-Cog that was greater than 30.

The way that I created the chart, it's in order. I just ordered it by the CGIC scores. So I wouldn't focus too terribly much on where in each one of those chunks at the 6, 5, 4, 3, 2, or 1, like where in that grouping each one of those individual subjects falls. I would focus more on the fact that you have -- so as you can see on the active side, you have three subjects who had a CGIC of 5 at 7 weeks, who had a baseline ADAS-Cog of greater than 30. And the remainder of them, the other five were at 4.

Similarly, on the sham side, one of the subjects who had a CGIC score of 6 at 7 weeks had a baseline ADAS-Cog of greater than 30. Two who had a CGIC of 5 were greater than 30, two at 4, and then three a CGIC of 3 at 7 weeks. So I understand it's a little bit difficult to walk through that.

DR. JAIN: And so the bottom line that I take away from this is that the CGIC results do not show that same consistent pattern of worsening that was apparent on the ADAS-Cog. I still am curious about the 12-week and whether there's any difference. The Sponsor's slide suggested that at 7 weeks, sham was doing worse on this measure. I don't know if you have the --

MR. MARJENIN: I will try and work on --

DR. JAIN: Thank you so much.

MR. MARJENIN: -- work on getting that for you.

They've got it for us.

So if you can pull that up, that's great.

I would say, I'm not going to draw any conclusions from that. We had not explored doing that sort of figure to show the CGIC as kind of the waterfall style plot. I'm just providing the information that was requested.

DR. JAIN: And I think the larger question for me is, is cognitive worsening considered an adverse event, and is there a category for that as an adverse event within the FDA's conceptualization of it?

MR. MARJENIN: I would probably defer to Dr. Brooks on that. In terms of what we saw as adverse events and what we considered adverse events for the purposes of the presentation, I don't believe that was one of them.

DR. PENA: But just to keep in mind, if the Panel has comments on that, for the Agency to consider, we would welcome that input as well.

DR. JENSEN: Dr. Bell.

DR. BELL: Karen Bell.

I just need a clarification from the Sponsor about in the countries where this is already an approved, available therapy, the EU, Australia, and Israel, after the 6 weeks of treatment is done, is this a one and done type of therapy and you never get it again? Or how is it used ongoing? I'm curious.

MR. BAROR: I'll defer that question to Dr. Pascual-Leone. But if we may, after he answers that question, if we may come back to your question with our data on that, is that possible? Okay.

Dr. Pascual-Leone.

DR. PASCUAL-LEONE: Thank you for that question. I think that goes along with Dr. Knopman's question also earlier in regards to the duration of the effect. And I think you heard from the Open Session from some of the doctors that presented that their experience is that they tend to reapply the stimulation or the intervention, on average, 6 to 12 months later. And so, you know, it's difficult to have very solid data because it was not part of the pivotal study. And so it is based on the clinical experience. There -- I think, I can walk through a couple of slides if you want, but the bottom line is that it's based on the clinical

experience in the various countries, as you suggested, and that patients derive a benefit that sustains for about a year, and then it lapses and they seek for restimulation or reintervention at that point.

To characterize that duration of effect, I think, would require a different type of study and would be a different indication than what was sought after in this study.

DR. ANDERSON: But the indication that you're seeking, it will not just be for a one-time therapy; it will be for ongoing as needed therapy within the parameters of the ADAS-Cog if that's what's used?

DR. PASCUAL-LEONE: I'm not seeking any indication so I would be --

(Laughter.)

MR. BAROR: I think, to make a claim regarding longer-term and repeated sessions, this is something that we will have to come up with another study design. We can share with you our views and as to what do we plan in terms of postmarketing surveillance study. If this is of an interest, we can show that, but I don't think this is what we are now claiming. Okay.

Dr. Lavin, please.

DR. LAVIN: A question -- Phil Lavin. A question that came up earlier had to do with the CGIC distribution. And I want to show you two graphs, one for the overall population, PE, that's everybody, as well as for the intended population subgroup.

So if I could have the third one, let's see, that one there. So I think that will work.

That one is the overall population, the PE population. And as you can see, if you look at that, 84% of the active versus 58% of the sham were basically either no change or improved at 12 weeks. So, and the Fisher test for that is 0.01. Post hoc, yes, but still significant and something to hang your hat on as one of the original, you know, effectiveness endpoints, secondaries. And as you can see, the large contribution, big

difference occurring for those with no change, at -- to category 4. And then if we turn our attention to the subgroup, you see very much the same thing.

If I can have the next slide. There it is.

Pretty much the same thing, same kind of p-values, very much the same type of chart for the subgroup.

DR. JENSEN: So, Dr. Bell, to your question, would there be specific time points that you would want to see, in a study such as this, past the 12 weeks, for when patients should be retested?

DR. BELL: It wasn't that I had specific parameters in mind. I was just curious. We're being asked to approve something for an indication without a sense of will it be repeated, this therapy? Will this therapy be repeated, or will we have any idea or control over if it gets repeated in the real world? I'm not talking about the data that they currently have.

DR. KNOPMAN: I completely agree with Karen's point. I had made the point earlier. I must say that I am really confused how we could even be looking at approval with a chronic disease, for a 5-week treatment with absolutely no evidence presented, no study done, to know what its long-term course is. And the comment by Dr. Pascual-Leone that, well, we know in depression that the effect lasts for 6 or 9 months is completely inappropriate with a completely different disease.

So I think that the absence of any evidence about what happens after 12 weeks is a major deficiency. And, in fact, what we know after 6 weeks is that it trended worse.

DR. JENSEN: Any other comments from the Panel about this? Anybody else want to weigh in? Any other questions for the Sponsor or for the FDA? Yes.

DR. ANDERSON: I had a question about the lack of interim analysis. Why was that decision made in the U.S. pivotal trial, not to have an interim analysis? And, retrospectively, what would you have done?

MR. BAROR: The U.S. data -- Moran, do you want to take that?

And I would like if we may go back to this issue of the long-term data.

DR. KNOPMAN: I didn't ask a question.

MS. PLOZNIK: So to answer the question about the about the interim analysis, interim analysis usually requires, it has its costs, I will say, with the sample size. Sample size, especially in Alzheimer's studies where recruitment is really, really slow, also means a much longer study, in terms of time. And we were quite confident that we will be able to show results with the 120, later on 130 patients.

DR. JENSEN: Any final questions from the Panel? Any discussion among the Panel members about any -- yes.

DR. ROSENBERG: Okay. I'm Paul Rosenberg from Johns Hopkins. I'm going to stick my neck out and just give my opinions. They are malleable to change with information. I'm sorry. Did I do something wrong? They're malleable to change, but let me just stick my neck out to get a brisk discussion going.

I have no problems about safety or study conduct. The problem that I see about approval is that these data are null on the primary outcome and two of three secondary outcomes. And in order for us to approve, we need to be strongly convinced by the post hoc analyses. Admittedly, they're not specified in the statistical analysis plan, and we'd have to be very convinced. I'm not. And let me just mention in a couple of words why.

First of all, in the terms of the post hoc analyses, the patterns between the studies are not consistent, and this adds to uncertainty. I appreciate the use of the words certainty and uncertainty throughout this because we're not, we're never certain. We're asking how much uncertainty there is. Just to give an example, the secondary outcome in the U.S. pivotal study, one of them was positive at 12 weeks, in Korea at 7 weeks. The U.S. pivotal study thus shows delayed effect. That would be really cool, but the Korea not. I am

uncertain about that.

But really, that's not all, and that's not for me the important thing. For me, the important thing has to do with clinical significance. There is no universal method, work flow for validating clinical significance. If you think about it, we don't -- there are many measures where we are guessing at these numbers in this exact question. What's the minimum clinical significance on the ADAS-Cog, I've run into a lot.

Admittedly, the cholinesterase inhibitors, which were approved, you know, 15, 20 years ago, whatever exactly, had a similar effect size. There were some -- there are some differences. Number one, they were pretty solid on both outcomes. Both outcomes, you know, they would have an ADAS-Cog and then some functional outcome like CGI. They were solidly positive on both outcomes in more than one trial, so we're not there yet here.

But the other thing is that was 20 years ago, and we have had a lot of opportunity to use these drugs in clinical practice. I'm going to stick my neck out and get it chopped off. In my opinion, these ADAS-Cog differences of 1½ and 2 points do not, are not clinically significant. And I'm deeply underwhelmed by their, by how good they are for my patients.

Like Dr. Sabbagh, like Dr. Knopman, like many people around this table, I'm deeply moved by my patients' frustration at treatment. But I don't think we're going to do them a service by approving if there's a lot of uncertainty with this one.

The thing I'm most deeply moved by, the one thing I really learned today, is that if we approve this, we are setting a precedent, and I'm not ready to. I'm malleable to change, and that's what I -- I just wanted to get it out there to get the argument going.

DR. JENSEN: Dr. Goodman.

DR. GOODMAN: Yeah. So I've been involved with clinical trial design and implementation for, I hate to admit it, for more than two decades. And one of the things I've learned from involvement in those clinical trials is when your prespecified primary

endpoint is missed, the only value of the post hoc analyses is designing the next study. And I think that's where we are.

I think that, you know, there's some sort of signal in here, from the post hoc analyses, and that might lead to say another study. I'm not going to sit here and design the study. I don't think that's our job. But it might -- certainly to a group that's below 30 on the ADAS-Cog scale. It might call for a different design in which the cognitive training is in both groups, and there's just the active TMS in one of them and the sham TMS in the other, because that's one of the concerns I have, and I would guess others share it, that it's very hard to disentangle whatever signal we think we're seeing, so even at the 12-week mark. If we believe that's real, how much of that has to do with the cognitive training that they received?

You know, I understand the rationale, scientifically, for combining the two, that you're trying to engage those circuits, as you're administering TMS. I understand that there was data from Beth Israel Deaconess that showed that there was a small effect with cognitive training alone and an enhanced effect when you combine them. So I understand why you did it. But I think we're left with a quandary right now in being -- to figure out how much of the effect that we think we may be seeing in the post hoc analyses is due to the cognitive training alone.

DR. PROSCHAN: I think it's important to note that it's not just that the prespecified didn't come out statistically significant. It nearly came out statistically significantly showing the sham is better than the real. So to me, it's not like, oh, well, gee, it didn't quite make it. It's peak was 0.07. No, it's 0.09 going in the wrong direction. I think, based on the, you know, based on this pivotal study, there's much more evidence for approving the sham than approving the real machine, the real pulses.

DR. JENSEN: Thank you.

Dr. Knopman.

DR. KNOPMAN: I would just like to emphasize what Wayne said to that. This is data that -- and I think the FDA said this, that is hypothesis generating, to do a study better. The Sponsor emphasized how much effort they put into designing their pivotal study, and yet they chose, as the outcome, the 7-week point that they now say, of course, that wouldn't work. That clearly seems to show to me that more work is needed in design.

I also have questions about feasibility. They talked about how difficult it was to do these kind of studies. How is this going to generalize in a larger population? I think that is also an important unanswered design question that needs to be addressed in a future study.

I'm very moved by the comments of the patients, and I think we all think there's probably a signal here. But I think it is up to the Sponsors to design a study that's large enough and thoughtful enough to be able to understand, or at least to have some signal about who those responders are. And I don't think we have any sense of that now. So I see the data here as being very useful for doing a larger and better designed study from what you know, what they know now. But I don't see how what we have before us is something that could be approved.

DR. JENSEN: Any other comments from any other panel members at this time?

(No response.)

DR. JENSEN: Okay. So what I'd like to do before we go into the questions is break now. We were supposed to break at 3:30, but we're going to do it at 3:20. So we'll be back here at 3:35. And then what we will be doing is going through the questions, as a group, and to give our recommendations to the FDA.

So let's go ahead and break now. Be back at 3:35.

(Off the record at 3:20 p.m.)

(On the record at 3:35 p.m.)

DR. JENSEN: Okay. If we could all take our seats. Okay. So at this time, we're going to focus our discussion on the FDA questions.

And panel members, you have copies of the questions in your folders. I would ask that each panel member identify him or herself each time he or she speaks to facilitate transcription. Although I will say, I'm going to try to do this a little systematically. So what we're going to do is we're going to combine, sort of, some of the things that we do. We'll often do is we'll talk -- each person will give their opinion, and then at the end, you know, we go back and we talk about the recommendations to the FDA.

Instead, what I want to do is I'm going to ask you your opinion, any recommendations you have about that question, and we will give it to Dr. Pena now, and that will sort of shorten the sort of summation time because we'll be summating each question. Does everybody understand that?

Okay. You'll get the hang of it as we do it. The other thing I want -- the first thing I want to do, I'm going to go out of order a little bit. I think the first question to ask is really the safety question. So let's just start with the safety question.

"Are the risks for the neuroAD adequately reported and characterized?" And we'll start over on this side down with our representatives from Industry, Patient, and Consumer.

Mr. Wreh, you don't have to expound long. I just want to know whether or not you think the risks for the neuroAD have been adequately reported and characterized.

MR. WREH: The answer is yes.

MR. TAYLOR: No comment.

MS. EDWARDS: I don't know that I am -- yeah. No comment.

DR. JENSEN: Dr. Duff?

DR. DUFF: I think that they are.

DR. JENSEN: Dr. Lyden?

DR. LYDEN: Can I pass for a second?

DR. JENSEN: Dr. Anderson?

DR. ANDERSON: I still have concerns that there hasn't been systematic surveillance of psychiatric side effects.

DR. JOHNSTON: I would say no.

DR. JENSEN: And do you have a comment with that?

DR. JOHNSTON: Yeah, I'm happy to comment. I don't feel like there's been complete reporting of the safety data in several of the trials that have been brought for efficacy data.

DR. JENSEN: In the pivotal trial, though?

DR. JOHNSTON: In the pivotal -- the U.S. pivotal trial, I had no concerns.

DR. BAXTER: With the pivotal trial, I have no concerns either.

DR. PILITSIS: Pivotal trial, no concerns.

DR. DORSEY: Pivotal trial, no concerns, but agree with Dr. Johnston about the other studies.

DR. GOODMAN: Ditto.

DR. KNOPMAN: Pivotal trial, no concerns.

DR. POSTMA: So with the safety indicators that were looked at, I have no concerns, but I struggle to ignore the 6-week primary endpoint results, where the test group seemed to be actually disadvantaged at that point, compared to sham. And just given that we don't apparently have strong data for TMS in this particular population and for this indication, that's a little worrisome to me.

DR. BELL: Pivotal trial, no concerns about the risk.

DR. PROSCHAN: I also didn't have concerns from the pivotal trial.

DR. ROSENBERG: Me neither.

DR. JAIN: In the pivotal trial, I'm concerned about the risk of cognitive worsening in subjects with more moderate levels of dementia. And I also agree with Dr. Anderson that the psychiatric side effects were not well characterized.

DR. JENSEN: Thank you. So, overall, the Panel agrees that with the pivotal trial, there were no significant safety concerns with the exception of the fact that the psychiatric side effects were not well characterized and that there was worry about cognitive worsening in the patients with the moderate group and that there was some disadvantage to the patients at the 6-week endpoint in the treatment group. Is that correct? Okay.

And in terms of the other trials, there is not enough data to make a determination about whether or not there was issues with safety.

Does that answer your question? Carlos.

DR. PENA: Yes, yes. Absolutely.

DR. JENSEN: Thank you.

Okay, so now we're going to go to the next question, which is "Does the U.S. pivotal study demonstrate a clinically meaningful benefit for the neuroAD as an adjunctive therapy?" And if you believe that it does not, what number would you think would be a meaningful benefit, and please give me your response with both the ADAS-Cog and the CGIC. And we're going to start with Dr. Jain.

DR. JAIN: So, in answering this question, I don't believe that the clinical meaningful benefit of the intervention is being studied effectively, in terms of its primary endpoint. A 1.5 change on the ADAS-Cog is likely not clinically meaningful, but there are clearly some patients who did better than that. And I think, in an exploratory fashion, I'd say the pivotal trial does show a signal for some clinically meaningful benefit in those patients. And for example, perhaps an ADAS-Cog of about 3 or so might be clinically meaningful if that were

established as a standard, or whichever standard is most appropriate based on a larger view of the literature. Then it would also establish a standard for cognitive worsening, relative to the intervention.

So I feel that there is an encouraging signal here. And yet, I can't ignore that the primary endpoint was not met.

DR. JENSEN: Do you have any particular number in mind? You said 3 for the ADAS-Cog. What about the CGIC?

DR. JAIN: I'm going to pass on that.

DR. ROSENBERG: I say no to clinically meaningful benefit, despite plenty of room for optimism. In terms of the numbers, if we were to predefine a response, I would go with ADAS-Cog change of 3. I actually think 3 to 4, maybe 3½, something in that range, but considerably more than the 2 we've discussed. I think you need to have a clinically meaningful response. You could combine that with a CGI improvement of moderate or marked. And I don't think you should -- I don't buy taking the mean of the CGI. It's a really fundamentally ordinal variable.

DR. JENSEN: Thank you.

Dr. Proschan.

DR. PROSCHAN: I don't see -- you know, I don't see how you can say, you know, a 1.4 is clinical benefit when you don't even believe the 1.4 or what, you know, because of the fact that, you know, you're cherry-picking which group, which time point. So if I believed that that was the real effect, I might be persuaded by it, but I absolutely don't believe that that's a real effect. I think if you, you know, if you cherry-pick, you're going to get a biased estimate of how good the effect is. So I don't believe the effect, and I don't see that they've distinguished the results from chance.

DR. JENSEN: Okay. Dr. Bell.

DR. BELL: So I don't think that they've demonstrated a clinically meaningful benefit in the pivotal study. In terms of the outcomes that could be used in future studies, looking at this same situation, because I am hopeful about the therapy, I would say that using a standard for the ADAS-Cog more along with what we use in drug trials, perhaps, no less than 3, and for the CGIC, going for at least moderate would be -- moderate change, I mean, would make more sense.

DR. JENSEN: Thank you.

Dr. Postma.

DR. POSTMA: I agree with the comments of the prior panelists. I think it's difficult to make any real strong statements about specific minimum amounts of improvement in the ADAS-Cog or in CGIC alone. But, in general, I agree with expert panel's assessment that generally an improvement of 4 to 5 points or so, in conjunction with corresponding improvements in quality of life could be considered clinically meaningful.

DR. JENSEN: Okay, thank you.

Dr. Knopman.

DR. KNOPMAN: I would say no. And I would have to say I think that the question is somewhat misframed because a numerical score after -- well, again, the fact is that the actual numbers were all non-significant for the way they powered the study. And as we talked about, the 6-week results actually favored sham. So if we imagined that their post hoc analyses had results that had any meaning for the future, even after 12 weeks, a number on an ADAS-Cog, as somebody who takes care of Alzheimer's patients, has been involved in clinical trials, is meaningless.

What I care about is, after at least a year, or 18 months, I want to see that that's sustained. And if it's not sustained with a single treatment, I need to know how many treatments they need to give.

So I don't think the question can be specifically answered from the data here because there aren't any real numbers. Generally speaking, after 18 months, and that denominator is important, or pick your number, a year, 2 years, that there ought to be a sustained, a benefit of some -- I would be happy with 3 points.

DR. JENSEN: And the CGIC, do you agree that it needs to be at least moderate?

DR. KNOPMAN: Well, the CGIC is a very insensitive instrument, and I think that after 12 months or 18 months, on a group-wise basis, if you got somewhere, even half of a rating point, groupwise difference, that would probably be clinically important across a population.

DR. JENSEN: Okay. Thank you.

Dr. Goodman.

DR. GOODMAN: So my answer is no, so that I'm quite uncertain about their being evidence of probable benefit because they missed their primary endpoint. I'm thinking, as I said before, and I think others have, that there probably is a signal in here somewhere, although it wasn't particularly robust. And I think that -- I'm not sure if a single endpoint is what's needed. I think that maybe there needs to be some -- although you're always forced to come up with, you know, a single time point. Maybe if it was prespecified that the primary endpoint was say 12 weeks, and prespecified secondary endpoint was 6 months, or a year, you know, then we could take some of the -- look at some of the durability of the effect and take it seriously and no longer consider it a post hoc analyses.

In terms of the magnitude effect, I'd just have to defer to the data that was presented here, and it looked like there was some consensus, both internally and from outside experts, that you need at least a 2 and probably a 3 to 5, in order for it to be clinically meaningful.

DR. JENSEN: Thank you.

Dr. Dorsey.

DR. DORSEY: So to the credit of the Sponsor's investigators, participants and their families, the study appears to be rigorously conducted. On the prespecified primary outcome, and on the prespecified three secondary outcomes, there is no significant benefit, nor is there any signal of benefit. Based on that, I don't see how you can conclude anything other than that the treatment's not effective.

Going forward, I think we need to move away from subjective, episodic, clinic-administered scales like the ADAS-Cog. We know they don't work. The definition of insanity is doing the same thing over and over again and expecting different results. Ninety-nine percent of clinical trials in Alzheimer's disease have failed. It's good evidence that we should change the way that we're assessing drugs and the way we're conducting clinical trials. We need to move towards more objective, frequent, and real world assessments of Alzheimer's disease.

I'm far more moved about whether someone can walk down a dock or down an aisle than whether they can recall 8 words or 10 words in a clinic, in an arbitrary time, in an artificial setting. We have the tools and technologies to measure social engagement, to measure conversations, to measure sociability, to measure activity. We should be using those and stop using scales that we know don't work. I don't think history is going to judge us very well about the ADAS-Cog 20 years from now.

DR. JENSEN: Thank you very much.

Dr. Pilitsis.

DR. PILITSIS: I agree with everything Dr. Dorsey just said. And, you know, I think -- I come at this from care of Parkinson's patients. And, you know, we've moved away a bit from the UPDRS, which is the Parkinson's rating score, to more of an on-time or off-time. You know, I think when people have days that are good days and days that are bad days,

they're often not going to go to the doctor on those bad days.

So I think we're already creating a bias there. And so there has to be something where it's, you know, over time, what does that marker look like and what really is meaningful, in terms of, you know, the days that mom is mom.

DR. JENSEN: Dr. Baxter.

DR. BAXTER: Sure. So I would agree with others, that we did not show, they did not show in the pivotal, the endpoint. And, but there's a -- I would agree there's a signal towards that, so -- and I would go along with the comments of exactly what Dr. Dorsey said, that for the outcome measures, that it would be maybe timing to look at something that is more reflective of showing the outcome that would be desirable.

DR. JENSEN: Excellent, thank you.

Dr. Johnston.

DR. JOHNSTON: So I would say no to clinically meaningful benefit for the pivotal trial. And for the post hoc, I would say that the level of uncertainty about whether the results are due to chance remains a substantial concern to me. And, again, I agree with Dr. Dorsey's comments about thinking about what outcomes would actually speak to us as clinical investigators, and speak to our patients and speak to their caretakers.

DR. JENSEN: Thank you.

Dr. Ellenberg.

DR. ELLENBERG: With the benefit of going to the end, I have reconfigured my answer. The no remains, but I want to take Dr. Dorsey's comments in tow. What I was going to say was that all I've heard during the day, or all I've seen during the day and through the reading of the materials beforehand, is a whole host of confidence intervals that appear to be overlapping. So I am not impressed with the way these differences, statistically significant or not, are the same. We're just not seeing a signal, in my view.

But if there is an argument that the signal exists, then it seems to me that we should go back to the drawing board in terms of redesign of the study. The original study had apparently too large expectation of the outcome. The original study was designed to detect a difference of 4 points, 6 points in the treatment versus zero points in the sham. That resulted in a small sample size, one of the things we're decrying as we go through the data that we're seeing today.

So looking at Dr. Dorsey's comments, which I think described the issues that we've all been seeing, I would say, if the signal is there, and the Sponsor wants to move forward, I would suggest a new study. Originally, I was going to suggest that it be a larger study to take account of detection of the original or the observed difference at 12 weeks. But I think, after Dr. Dorsey's comments, I would reconfigure that to say the new design should account for possible composite endpoints, possible more comprehensive evaluation, taking clinical aspects into account, rather than just standardized testing.

And I would want to see a component of the design that looks at the differences in the equivalent of a drug-free population, or a population that's stabilized. The difference in ADAS-Cog score, if that were chosen, over time, as a basis for how you design the clinical trial that's trying to detect differences, that would be better in the negative direction than we see in a normal placebo group.

So the simple answer is no, and I'd like to study redesign based on Dr. Dorsey's comments and much of the comments made today throughout the Panel.

DR. JENSEN: Thank you very much.

Dr. Anderson.

DR. ANDERSON: So I agree with the other panelists for the U.S. pivotal study. I don't see a clinically meaningful effect. However, I would encourage the Sponsor to redesign another study. I think there is a positive signal there. I absolutely agree the ADAS-Cog is

not going to get them there, and they need to think about some more dynamic measures.

DR. JENSEN: Thank you.

Dr. Lyden.

DR. LYDEN: So, yes, the pivotal study failed on its endpoint, and there's no clinically meaningful benefit there. With respect to the minimum amount of improvement, I had this question in front of me as the patients and families were speaking earlier today. And it occurred to me that that's the answer.

I am a stroke neurologist, but I take care of a lot of dementia patients. In fact I'll, like so many of you, be going home tonight, and clinic tomorrow is a hundred percent dementia. And I'll be spending the weekend as a caregiver, with a mother and a mother-in-law who are going through what many of you have eloquently described as well. And my patients would gladly fly to Australia for a treatment. Many of my patients take a day off work and change buses three times to come see me.

And I think the Sponsor needs to listen both to the patients that have spoken here today and the broader community that will do anything. They truly feel they have nothing to lose. So the clinically meaningful benefit is that benefit that the family can count on as being beyond the variation that is part of this disease, which was alluded to earlier, but only briefly.

There's a day-to-day variation, a month-to-month variation, a year-to-year variation. And I don't know the standard deviation over time of these studies, but it seems to me like what some of the findings are is within variance that occurs over time. So the clinically, the minimum benefit for my patients is anything, anything at all, that they can be sure of isn't just random chance.

DR. JENSEN: Thank you.

Dr. Duff.

DR. DUFF: So I think the CGIC is actually the measure that stood out to me the most. Even though, as a neuropsychologist, that's not my favorite type of measure, but as a clinician looking at somebody and saying, are they the same, are they better, are they worse? And they are ordinal -- it's an ordinal scale. And if you ignore sort of rounding because you're averaging together scores, basically they're all 4s. Both groups gets a 4, which means somebody has looked at them and said there's no change.

And so it's hard to move beyond that for me. I agree that the ADAS-Cog is probably not the right scale for this study. We heard from Dr. Schneider how it was developed. It was developed in patients with mild to moderate Alzheimer's disease, to identify the deficits that we see in those patients. But then we heard from Dr. Pascual-Leone that said, these tasks aren't really necessarily designed for Alzheimer's disease, so maybe we shouldn't expect to see a whole lot of change on it.

So maybe it was a poor choice of the ADAS-Cog as an outcome measure, but I feel bad because all clinical trials in Alzheimer's disease use the ADAS-Cog. Yes, we could be recommending that this study team and many others completely reinvent the wheel and do things that's never been done before. But that's going to take a big effort in the field to really change that.

Yesterday, I was back in Salt Lake City reviewing grants for NIH, a teleconference before I flew out here. And most of them included things like the ADAS-Cog or the CGIC because that's what reviewers expect, you know. So I feel like we're sending a mixed message to the Sponsor of how they should design the next trial. I do not disagree at all with Dr. Dorsey that we need to do better things. I don't know that ADAS-Cog is definitely it. But for me, this particular one, the CGIC actually means the most. And so based on that, I'd say the pivotal U.S. trial doesn't provide clinically meaningful benefit.

DR. JENSEN: Thank you all very much. That was very robust, and I'm hoping I'm

going to get all of the recommendations correct, to Dr. Pena.

So, Dr. Pena, the group agrees that the U.S. pivotal study did not demonstrate a clinically meaningful benefit for the neuroAD as an adjunctive therapy. This is primarily based upon the fact that they did not meet their primary endpoint, and to most of the group's mind they did not meet the secondary endpoints either.

However, most of the group believes that there is a hopeful signal that came out of this trial, although there are a few people on the Panel that don't see that signal. And in moving forward, if one is forced to use the standard tests that are currently being utilized, meaning the ADAS-Cog and the CGIC, then a number that is more along the lines of meaningful benefit would be no less than -- has to be at least 2 or greater, and somewhere between a 3 to 5.

Other panel members -- the Panel members also feel that the CGIC, with one panel member in particular thinking that being the more important scale, feel that there needs to be at least a moderate or marked change in order for this to be a clinically meaningful benefit.

However, as we all heard in the discussion, do these scales actually identify a true meaningful benefit in the way that is meaningful to the patient and to the patient's family? And so, ideally, one would want to see the testing move more towards an objective score of more relevant activities, such as social engagement, conversation, etc., that is really truly meaningful. So that is, I think, the best answer that we can give to this question at this time.

DR. PENA: Thank you. That's clear.

DR. JENSEN: Okay, the next question. "Where the neuroAD is used as an adjunctive therapy, what minimum amount of improvement in ADAS-Cog alone is clinically meaningful, as well as what is the minimum amount of clinically meaningful improvement in the CGIC?"

And I believe that we have answered that question in conjunction with the previous question. Does anybody have anything else to add to that?

(No response.)

DR. JENSEN: No. The next question, "Is the ADAS-Cog ≤ 30 population, is that a clinically plausible subset and can patients be screened using the ADAS-Cog for the neuroAD?"

So I think we'll start over here with Dr. Duff.

DR. DUFF: So optimistically, I think yes, they can be screened with the ADAS-Cog, but as I brought up earlier, I think this less than 30 is a very narrow window that's going to be really tricky for people to identify. It's a 12-point range, from 18 to 30, which is again, is about 3 points on the MMSE. So picking patients that fit into that narrow window, for long enough that you can enroll them, and get them into a treatment, is going to be challenging. So I see it as incredibly difficult, maybe more possible than plausible.

DR. JENSEN: Is there some other window that you would recommend, or consider?

DR. DUFF: I mean, I think it would be based on different criteria, not on a narrow window of ADAS-Cog scores.

DR. JENSEN: Okay. Dr. Lyden?

DR. LYDEN: Agree, it's not clinically plausible.

DR. ANDERSON: I also agree, and I think, as was mentioned earlier by Dr. Duff, it's not used clinically much, so it's going to be really difficult for practitioners to understand what patients might be appropriate if this is ever approved.

DR. ELLENBERG: No comment.

DR. JOHNSTON: I would say not plausible, and combining those comments that if there is a subgroup to be selected, it should be considered during trial design, about how the clinicians are seeing the patients, and what could be used in a clinical environment.

And that's what should be used in the clinical trial to define the subgroup, as opposed to a research-based subgroup, the ADAS-Cog ≤ 30.

DR. JENSEN: So what sort of clinical --

DR. JOHNSTON: So something like -- and I'm not a memory disorders person, but something that clinicians would use, like the Mini-Mental Status or a bedside cognitive exam that clinicians are used to using and would be able to use in normal practice to identify the population, so if and when the treatment was offered, they could identify them easily and reliably.

DR. JENSEN: Thank you.

Dr. Baxter?

DR. BAXTER: Agree with that as well, that it would be something that -- I agree that this is not plausible. It'd be something along those lines of using something that would clinically be very, you know, identifiable and easy to recognize.

DR. JENSEN: Thank you.

Dr. Pilitsis.

DR. PILITSIS: Agree.

DR. JENSEN: Dr. Dorsey.

DR. DORSEY: So it's just not widely used right now. I think if you're thinking like should we look at early Alzheimer's disease like early Parkinson's disease or early degenerative disorders, that might be reasonable. I don't have a great feel for the mechanism of action of the intervention. But most interventions aimed at neurodegenerative conditions are looking at earlier populations, and that might be one way to go.

DR. JENSEN: Dr. Goodman.

DR. GOODMAN: So I agree with the other comments, that it doesn't seem to be

clinically feasible. Also, I think somebody raised the concern earlier, and I share it, that if you take somebody who's got ADAS-Cog score above 30, that you might actually make them worse, that gives me some concern. I mean, you know, I certainly can understand that it might not help them, but with that there's also a possible risk it may make them worse, makes me very uncomfortable.

So you really, it sounds like you would really have to get that range just right. And not only might it not work, but they're going to have -- you're going to make their condition worse after 6 weeks of intensive treatment.

DR. JENSEN: So you would be concerned about what would be considered now the moderate group?

DR. GOODMAN: Yes.

DR. KNOPMAN: So I agree that the ADAS-Cog is simply not used in clinical practice. What is used in clinical practice are categorical diagnoses of mild -- of cognitively unimpaired, subjective cognitive impairment, mild cognitive impairment or dementia. And the way that the bulk of the therapeutics field has gone is to look at people in the MCI and mild dementia range that are defined by a Mini-Mental State, but also usually -- or a MoCA or even by this test, the ADAS-Cog, but only after the categorical diagnosis is first applied. And the categorical diagnosis is actually very important, of MC, mild cognitive impairment, minor neurocognitive disorder and DSM versus dementia. So the answer to this is no.

DR. JENSEN: Dr. Postma.

DR. POSTMA: Pass.

DR. JENSEN: Dr. Bell.

DR. BELL: I don't think that it's plausible to use the research tool, the ADAS-Cog in a clinical setting to identify the range of patients who would be eligible for the intervention.

DR. JENSEN: Okay. Thank you.

DR. PROSCHAN: So I don't think I can really answer this question. I did want to comment just briefly though, about the greater than 30. You know, it's not necessarily that, you know, this is causing harm in the greater than 30. You know, I don't know that this different cognitive training couldn't have made that difference. Maybe listening to music and watching nature programs actually helped them more than what the usual cognitive training was.

DR. JENSEN: Yes, sir. Dr. Rosenberg.

DR. ROSENBERG: I think ADAS-Cog is a research tool that can be used to bridge to clinical tools. So I would encourage, if there was another study, to actually look at ADAS-Cog ≤ 30 as an entry, just to translate from the study to the next, but then to use widely clinically available tools.

I agree with David's point. Most studies are basically lumping together prodromal Alzheimer's and mild Alzheimer's, and frankly, the categorical definition is probably a stronger way to define it.

DR. JENSEN: Dr. Jain.

DR. JAIN: One of the Sponsor's appendices provided rates in highly selected clinicians of use of the ADAS-Cog, which doesn't map onto my clinical practice either. I think it really is not very widely used in clinical practice. And it sounds like a substantial proportion of the Panel doesn't think that it's very good as a research assessment. So translating that or training clinicians then to use the poor research assessment seems like a step backward.

DR. JENSEN: Thank you.

So, Dr. Pena, the Panel's response is that the ADAS-Cog ≤ 30 population is not a clinically plausible subset, and that instead of using a research tool, instead that people should be identified as possible subjects using categorical diagnoses, and that clinically

relevant examinations, such as the MMSE, that clinicians are used to using should be used instead.

DR. PENA: Thank you.

DR. JENSEN: The next question is, "Is the post hoc identification of ADAS-Cog ≤ 30 population at a later time point when no treatment is given an adequate analysis of the pivotal study data, in concert with the supplemental data provided, to demonstrate probable benefit?"

So let's start with Dr. Jain.

DR. JAIN: No. I don't believe so. And it's concerning from a mechanistic standpoint that within the supplementary data, improvement happened at a different time course as in the pivotal study.

DR. ROSENBERG: No. And most rTMS therapies don't have delayed benefit. Dr. Pascual-Leone pointed out a couple that did.

DR. JENSEN: Okay.

DR. PROSCHAN: No.

DR. JENSEN: Thank you.

Dr. Bell.

DR. BELL: No, I don't think that it provides the -- I don't think that the post hoc analyses is useful other than in identifying that additional study needs to be done.

DR. JENSEN: Thank you.

Dr. Postma.

DR. POSTMA: I agree with Dr. Bell, no.

DR. JENSEN: Dr. Knopman.

DR. KNOPMAN: No.

DR. JENSEN: Dr. Goodman?

DR. GOODMAN: No.

DR. JENSEN: Dr. Dorsey?

DR. DORSEY: No.

DR. JENSEN: Dr. Pilitsis?

DR. PILITSIS: No. And I would just take it one step further that, you know, though I'm hopeful about a signal, I'm not sure that focusing on this is necessarily the way to go, alone.

DR. BAXTER: No as well.

DR. JENSEN: Dr. Johnston?

DR. JOHNSTON: No.

DR. ANDERSON: No.

DR. LYDEN: No. I like Dr. Bell's point, that this is an excellent place to start the next study.

DR. JENSEN: Thank you.

DR. DUFF: I did want to be hopeful about that delayed sort of response, that maybe while you're going through TMS, maybe it does sort of confuse you a little bit, and the response doesn't show up until actually it stops, and some consolidation happens. And I really like that sort of hypothesis in my head, just looking at their data. But when you add in the Korean data and the other data, where they show no benefit over time, that sort of led me back to sort of the original, and I guess sort of somewhat consensus here of no benefit.

DR. JENSEN: So, to the FDA, the Panel is unanimous in that the post hoc analyses was not useful except to be a good starting point for the next study. In terms of time points, as a previous -- and we were discussing previously, it would be useful to have prespecified time points that extend beyond the 12 weeks, as far out as up to 1 or 1½ years,

with another trial design.

Does that answer your question?

DR. PENA: Yes, thank you.

DR. JENSEN: Okay. This is the last question. "Do the probable benefits to health outweigh the probable risks?"

And we'll start with Dr. Duff.

DR. DUFF: No.

DR. JENSEN: Dr. Lyden?

DR. LYDEN: No.

DR. JENSEN: Dr. Anderson?

DR. ANDERSON: No.

DR. JENSEN: Dr. Johnston?

DR. JOHNSTON: No.

DR. JENSEN: Dr. Baxter?

DR. BAXTER: No.

DR. JENSEN: Dr. Pilitsis?

DR. PILITSIS: No.

DR. JENSEN: Okay. Dr. Dorsey?

DR. DORSEY: No.

DR. JENSEN: Dr. Goodman?

DR. GOODMAN: No.

DR. JENSEN: Dr. Knopman?

DR. KNOPMAN: No.

DR. JENSEN: Dr. Postma?

DR. POSTMA: No.

DR. JENSEN: Dr. Bell?

DR. BELL: No.

DR. JENSEN: Dr. Proschan?

DR. PROSCHAN: No.

DR. JENSEN: Dr. Rosenberg?

DR. ROSENBERG: No.

DR. JENSEN: Dr. Jain?

DR. JAIN: As the final question that we're going to respond to, I want to put it into a bit of a broader context. I think no from the statistical standpoint, and yet we've heard from a number of patients today a different experience of this treatment. And we also heard from Mr. Taylor regarding his own experience with his wife.

And I just want to take a moment as well to applaud your strength in being here despite receiving the news today that the trial that she's in is being stopped, you know, and your desire for a kind of third way forward for those who want to seek aggressive treatment.

I would point to the potential of the Right to Try legislation as potentially being helpful in that regard. But on the basis of the evidence that I saw today, I wouldn't want this being marketed to my own grandmother, who had dementia, as something that my uncle would have had to bring to her every day for 6 weeks for 3 hours a day.

So while I feel there is a signal, I'm really hopeful that it will continue to undergo further development, I'm a no on this as well.

DR. JENSEN: Thank you very much.

So, to summarize the Panel's finding, the answer to this question is no. However, all the Panel members here deeply feel about patients, family members. It's a difficult topic. We want very much for there to be a treatment that is effective, and we really hope that

you continue to bring forward trials that give us the data that will allow all of us at this table to say, resoundingly, yes.

So at this time, the Panel will hear final remarks from the FDA. You have 5 minutes.

DR. PENA: So thank you very much for the discussions. You know, I started out the intro at the beginning of the meeting where we stated Alzheimer's disease is important to FDA. Patients with this disease are important to FDA, and assuring patients in the U.S. have access to medical devices that have a reasonable assurance of safety and effectiveness is equally important. And I think that's sort of something that we continue to believe.

We will fold your discussions and deliberations into our review. And thank the Panel, the patients, and the attendees at today's conference. Fold that discussion and those comments into our deliberations.

Thank you.

DR. JENSEN: At this time, the Panel will hear final remarks from the Sponsor. You also have 5 minutes.

MR. BAROR: Thank you very much, everyone, for the time, and thank you for the comments. I think we will review them internally and consider how to address the concerns that was raised. I am happy to see that at least on the issue of the safety, there is some form of acceptance of the safety of this therapy.

Yet again, we will take all the comments that we have, that we have received, and we will consider these things, going forward. As mentioned again and again, the system is currently approved outside of the U.S. We'll have to see what do we wish to consider, moving forward, because I do think that eventually American citizens should be allowed also rapid access to such technologies, such or other technologies, and not just people out of the U.S. But in any case, I think we will definitely all agree that Alzheimer is a huge issue, that everyone has to find ways to tackle.

And thank you very much, everyone. And above all, thank you to patients.

DR. JENSEN: Yes. Thank you very much. I would like to thank the Panel, the FDA, and the Sponsor for their contributions to today's panel meeting.

Dr. Pena, do you have any final remarks?

DR. PENA: No.

DR. JENSEN: This meeting of the Neurological Devices Panel is now adjourned.

(Whereupon, at 4:19 p.m., the meeting was adjourned.)

# C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

March 21, 2019

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter