Zoom In on **Dementia & Alzheimer's**

The HOPE Study: Testing a Non-invasive, Light and Sound Stimulation Treatment for Alzheimer's
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Transcript of Zoom with Brent Vaughan, Chief Executive Officer of Cognito Therapeutics

Please note: This transcript has been edited for clarity and brevity.

NANCY LYNN: Welcome, folks. Good morning and good evening or afternoon, wherever you are. My name is Nancy Lynn. I'm senior vice president for BrightFocus Foundation. And BrightFocus Foundation funds research globally for Alzheimer's disease, macular degeneration and glaucoma. We've been around for 51 years. We have just passed the threshold of funding $300 million of research globally. And so we are delighted to be bringing you this Zoom In on Dementia and Alzheimer's Clinical Research series, which is supported, in part, by educational funding from Biogen, Lilly and Genentech.

And this series, this is only the second episode in this series, is designed to not only bring you information about trials and studies for Alzheimer's disease, and sometimes related dementias that are actively recruiting, but also to help everyone really learn what is a clinical trial, what's the process, and give you the opportunity, because it's so hard to find sometimes, and understand the whole process of being in clinical trials and finding a location near you. And so really to understand that and the

phases of clinical trials.

I'm going to jump in and introduce our guest, Brent Vaughan. Brent Vaughan is chief executive officer of Cognito Therapeutics. He has more than 20 years of experience as a serial founder and leader of teams developing proprietary technologies and innovative health care products across multiple domains, including pharmaceuticals, medical devices, and digital therapeutics. Prior to Cognito, Brent was chief executive officer and co-founder at Cognoa, an AI-based digital therapeutics company where he established the company as a leader in digital therapeutics and pediatric behavioral health. Under his leadership, Cognoa was awarded FDA breakthrough designation for the first two products for autism, and successfully completed the clinical development of the lead product. Brent was also co-founder at Wellness FX, a leading digital health company. Welcome.

BRENT VAUGHAN: Thank you very much, Nancy. Thanks for having me here.

NANCY LYNN: Thank you for being here. I'm going to jump right in and ask you about the HOPE Study. But before I get to the HOPE Study and its predecessor, the OVERTURE Study, let's talk about your device, your technology. So this is not a drug trial, this is a trial that is testing a device called Spectris. So what's the device, and what does this device do, what is it targeting?

BRENT VAUGHAN: Excellent. Thanks so much. And thanks, everyone, for joining and listening in. So Spectris is a device intervention that is designed and intended to treat and slow the progression of Alzheimer's disease in the same way that we've always thought of drug-based therapies, but we do this without actually administering a drug. And the science behind it, I think your audience might find quite interesting, for decades, we have taken for granted that changing the chemistry in the brain will change the electrical activity. And the electrical activity in the brain, that is who we are, that is what we remember, that's how we act. And what we've learned at Cognito, and the basis for our technology, which was groundbreaking research that was done at MIT, and we've worked very closely with the original scientific discoverers at MIT, who lead our Scientific Advisory

Board, we found that as much as changing chemistry can ultimately change the electrical activity and performance in the brain, and this is how the first generation of Alzheimer's drugs worked. Drugs like Aricept, increased neurotransmitter levels, which is a chemical change, and that allowed people to have change in performance for cognition, for memory, for function. What the researchers at MIT learned early on is that this is actually a two-way street. And you can modulate the electrical activity in the brain. And not only does it just change function, but it also can change the chemistry and the biology. 20 years ago, I was working in a company where we advanced two small molecules into Phase 2 for Alzheimer's disease. And those early drugs had a lot of promise.

What we do with Spectris is, we modulate the electrical activity in the brain. And we've been able to show that changes biology and creates long-term outcomes, which we saw in our Phase 2 study, which is slowing of disease progression, similar to what people are trying to do with drugs, but with a very, very different side effect profile. And so a side effect profile that is quite benign. We saw no treatment limiting serious adverse events in our six-month Phase 2 study.

NANCY LYNN: I'm going to jump in, because I'm going to do this very conversationally. And you all can feel free to jump in as well, or type something into the chat, and I'll read it out. But so you're talking about your device, and we're going to talk about what it does, that it can affect electrical activity in the brain. So does that mean that something is going wrong with your electrical activity in the brain with Alzheimer's, because that's not what we usually hear scientists talking about. We're talking plaque, tangles.

BRENT VAUGHAN: Yeah, that's an excellent question. So when we hear people talk about tangles and plaque, part of the reason we focus on those proteins in Alzheimer's, is because when they accumulate in the brain, they start to affect the electrical activity in the brain. And that's what's changed its function. One of the early experiments that helped us understand this, is when you do an EEG of patients, and then they're matched nonpathological cohort. So a patient, and then a similarly aged non-patient, who does not have Alzheimer's disease, you can

see differences in the brainwave activity. And one of the early learnings was, there's a certain frequency of activity in the brain that is relatively missing in the Alzheimer's patients. And this is the activity in the gamma frequency, so normally our neurons and synapses are oscillating at different patterns. And when people develop Alzheimer's, and you see this in the animals as well, as the Alzheimer's progresses, you start to see less and less gamma activity. And so our original premise was, is there a way to restart that gamma activity, and would that help? And lo and behold, we found A, you can restart it, and B, it seems to have a durable effect to slow the progression of Alzheimer's and allow people to maintain function.

NANCY LYNN: I think I heard you say something that I didn't see on your website, and that is that, and correct me if I'm wrong, that the sticky proteins that are often found with Alzheimer's may be part of interrupting the gamma waves, or the electrical functioning in the brain. Would that mean, ultimately, that this type of treatment could be used together with the new drugs that are out, and that together, they might have an even greater effect used together?

BRENT VAUGHAN: That's a great question. The science all points towards that there is a strong likelihood that these would work together, and that they would work synergistically. We target a different thing, the anti-amyloid antibodies, so Leqembi, which was approved about a year ago, and Kisunla from Lilly that was approved recently. They target the plaque that accumulates, and they look to remove that plaque from the brain. We do not target the plaque, we target the underlying degeneration, so the loss of brain structure. People with Alzheimer's, their brain shrinks and loses structure at three to four times the rate of just normal aging, and we slow that down. And when we preserve brain structure, it preserves function, which is the slowing of disease. But that is completely, we believe, parallel to what the new antibody drugs do. So we have not done a study looking at the two drugs in combination, it is certainly something that we'll be looking into in the future.

NANCY LYNN: That's actually quite exciting, even for people like me who've been doing this for 15 years. So I wrote a note to myself. The Spectris system could provide disease-modifying therapy for treating

Alzheimer's disease. It's a noninvasive, neuromodulation device, and we're talking about the headset and glasses, delivers proprietary gamma frequency, light and sound stimulation. So can you describe what it's actually doing?

BRENT VAUGHAN: There were a lot of big words in there, so let me try to break that down a little bit. The device is designed to be used at home. So in our clinical study, which I know we'll be talking about a little bit later, but we have patients who use this every day. They get up in the morning, they put on a headset. If you go to the website, you can see some of the different design styles of our headset. Patients put on a headset, they sit down in their favorite chair, or sit down on the couch. They wear it every day, they take it off, put it back on the charger, go about their day. So when they put that on, so this is instead of taking a drug, when they put it on-- what we do is we have certain frequencies of light and sound. And so when we talk about trying to turn this particular brain frequency activity, and get it to restart in these Alzheimer's patients, what we found is that if we provide certain frequencies of light and sound, we stimulate the visual cortex and the auditory cortex of the brain, and it gets the brain to restart these very important oscillations in the gamma frequency. So our dose for people is for people to put on a headset, and the headset has earphones built into it, it has eyewear built into it. And we can use an oscillating light, and an oscillating sound to recreate that electrical activity in the brain that is depressed or missing in Alzheimer's patients. And when we do that, it restarts some of the important biochemical reactions in the brain that allows us to preserve brain structure and brain function.

NANCY LYNN: Thank you. Really fascinating. So the questions are already pouring into the chat now. So Elizabeth writes, is there a time when what you are sharing, and the effect of this device won't be as effective, because you waited too long. And so that leads me to one of the first questions I was going to ask, at what time in the progression of Alzheimer's do you think this device will work, and I'll let you say what you're testing in the HOPE Study. And then also, do you think after the HOPE Study, you might test it in other phases?

BRENT VAUGHAN: So at the top of the chat, people will see the link for

the HOPE Study. There's lots of information there about the HOPE Study. For those who can't see the chat, it's just simply www.hopestudyforad.com, for as in the word for, not the number. But if you were to Google HOPE Study for AD, you will see the landing page there as well. You can see on the page that we're enrolling patients between the ages of 50 and 90, so it's very broad. If you look at Alzheimer's studies and Alzheimer's therapeutics, they have a tendency to talk about mild or moderate Alzheimer's patients. The recent antibody studies have focused more on mild patients. We're actually enrolling both mild and moderate patients. So patients that are possibly too progressed or too far along for some of the antibody studies over the last two years may very well qualify as a moderate patient for our study. So I encourage them to go to the site. We have almost 60 centers across the United States that are enrolling, so there is one in almost every major metropolitan center. So when you go in, it will take you through a series of questions, and you can find a study near you. But right now, we are focused on mild and moderate, which is a pretty broad spectrum of Alzheimer's population. And in the future, depending on how the study goes, we could see that, maybe going even into earlier stage patients, but we're just not there yet.

NANCY LYNN: I'm interested whether it might even be used before you have symptoms, and if you, at some point, might be able to measure electrical activity going awry, and use it, but I'm sure we can't answer that yet. Let's see. Well, I was going to get to the specifics of the trial, but-- Oh, I know, I wanted to mention to everybody that, when we're talking about mild and moderate stage, that may or may not mean something to doctors and clinicians in the field, because it's very confusing to try to understand. If you go online, you'll see there's three phases, or there's nine phases, or there's five phases. And so we actually have a recorded episode of the Zoom In on Dementia and Alzheimer's, that is with Dr. Marwan Sabbagh, about what are the stages of Alzheimer's? So if you have questions, you will be able to send them to us, but you might want to watch that episode, because it will discuss what does it mean to a doctor, or for a clinical trial to be mild or moderate rather than advanced, even though we think we know what it means. They're doing it by ratings on a test, basically.

BRENT VAUGHAN: I did not realize you had that, Nancy, but Marwan is one of our medical advisors, and we know him quite well. And he is an

excellent resource for your community.

NANCY LYNN: Yes, he is fantastic. And I should mention that we have over a dozen episodes on all different subjects on the website available for free, if you want to look. Some of them pertain to this quite closely, in particular Randy Bateman's episode on how do you get a diagnosis. Because it's actually incredibly difficult just to go through the process of getting a doctor to know really. They don't know what exact tests are needed, and how to differentiate when you should just go home, and come back in a year, or when you really should start getting further testing. So Randy Bateman's episode is really excellent for that, if you want to learn more about that. And Bert's YouTube question, I'm going to get to it. Let me jump into the trials now. So you did, before the HOPE Study, a Phase 2 study, called the OVERTURE Study. And for the benefit of the audience, what is a Phase 2 study? So trials are generally done in three phases, sometimes there's a fourth phase. And the first phase is really to make sure that the drug is safe to take. And so will you explain, Brent, what is a Phase 2 study, your OVERTURE Study?

BRENT VAUGHAN: Certainly. And to make it even slightly more confusing, the people in the device world use slightly different labels and names, than the people do in the drug world. So we sometimes lump them together. But there's even more levels of complexity here. But you are right, when you think about doing these studies, they really come in three phases. Number 1 is about safety, and that's usually what we think of as a Phase I study. And usually you just show that something is safe, or understand the limits of safety, what's the highest dose we can give a patient before we start to see real side effects. So you establish your safety window. Your second stage, which is often referred to as Phase 2, is your human proof of concept. And so that's usually the first time you go into patients, and you show whether or not there's a treatment effect. And so usually, like with us, there was pre-clinical data done in animals showing that the animal models of Alzheimer's were able to dramatically slow or reverse the progression of Alzheimer's in the Alzheimer's mice.

The Phase 2 study is when you first go into actual Alzheimer's patients and show whether or not you can have a treatment effect. And so when

we did that in our OVERTURE Study, which was one of our Phase 2, or our human proof of concept studies, we had just over 50 subjects that used the product for six months. So it was a blinded study. So we had two versions, we had an active version and an inactive version of the device in the same way in a study, you would have a drug or a placebo, so very analogous to that. Patients and their doctors don't know which one you're on, because that would bias the study if you knew if you were getting active or not.

And so we had a study with roughly 60 subjects. They were blinded and randomized into either an active or a non-active device at the end of that. So when you do that, you get a very powerful result. You get to see the patients that are on your placebo or your inactive device, and you get to see the rate at which they decline with Alzheimer's. And then what you're hoping for, is the patients on the active device. That line diverges, and that line doesn't show as much decline. And you're hoping to see these two lines diverge over time. And that's exactly what we saw. We saw the patients that were on the active device across six months had a greater than 75% slowing disease progression. And so they retained 75% of that baseline function, versus the patients that didn't get it at all. And they did that all with no treatment-limiting serious adverse events, which means no one had a serious side effect that made them come off therapy across that six months.

NANCY LYNN: So I'm going to go back. So the Spectris was used at home by people for six months, around 60 subjects, you're saying, some of whom had the active device, and some of whom had a device that wasn't really active. And after the six months-- Personally, I was astonished by these percentages, and I wrote it down. So the three things that were being measured were, preserving the brain volume and structure, so actually the physical volume of the brain, and we'll go to that. The second was preserving cognition, and there are cognition tests, some of you may have taken them, that can say if you're preserving that function, or if it's getting worse, of what you can remember or your thinking. And the other was preserving function, which has to do with your ability to do activities of daily living. So it's one thing if you're able to recall 10 words or three words, it's another thing if you're still able to put on your socks and shoes, and find your way to the grocery store. So those are the two

different things they're measuring for. And so tell me if I got these wrong, but I got them off your website. I have 77% reduction in the decline, so in the rate of decline of daily functioning, just to me seems really great. 76% reduction in decline of cognitive function, and you're thinking in your memory, and 69% reduction as shown on MRI in brain volume loss. So can you teach us about brain volume loss, is that normal?

BRENT VAUGHAN: For sure. And maybe I'll touch on the other two first. So our primary endpoints for our pivotal study, which is Phase 3, which we didn't talk about before, but that's where we are now. After you establish safety in Phase 1, and human proof of concept in Phase 2, usually go on to what's a Phase 3, or a pivotal study, which is the study you submit to the FDA for approval. So that's where we are right now, we're enrolling that study. It'll be 12 months on treatment, not six months, but everything else, very, very much the same as what we did in our Phase 2, because our Phase 2 showed such a great effect. We just need our Phase 3 to look like our Phase 2. So in that Phase 2 study, there's both the cognition measure. And so there is a scale that is used by neurologists called the Mini Mental Status Exam, and they abbreviated the MMSE. It is the tool that's most commonly used by neurologists in the US to diagnose and track progression of patients. And so we use the thing that neurologists are most comfortable with, and that really focuses on cognition, which is the ability to recall things. But we do a lot more with our brains than remember lists of numbers, phone numbers, and lists of words.

And so the things that we do with our brain involve sometimes more complex functions. And so the second endpoint that we use is called the activities of daily living. And to give you an idea for something like a cognition scale, like an MMSE, at the beginning of the interview, they'll give you five words, for example, and one of those words might be keys. And then after going through the other questions, they'll come back at the end and say, how many of those words from the beginning can you remember for us. And if you remember keys, you get a point. In activities of daily living, they ask you and your care partner, can you still find your car keys? Can you still do your hobbies? Are you still able to get up in the morning and make breakfast? If you like to knit, are you still knitting? And so activities of daily living get more global function, which for most

families, for most physicians, and actually, even for most of the payers and insurers, those functional measures are actually a little bit more relevant than how many names or numbers you can recall. And so those are the first two.

The third one is quite unique to us. Since we are not targeting plaque, or amyloid, we're not targeting tau, but we're targeting this underlying loss of brain structure. We use MRI, and we use an MRI, so it takes a type of picture of the brain. And then at the end of the study, we can take a picture of the brain, and we can measure how much the brain has shrunken or atrophied in between the two time points. So there is no subjective measure here, there's not good days and bad days, it's a very objective measure of progression. And other treatments that have been out there have never been able to show a real change in the ability to slow this loss of brain structure and brain volume. And we've been able to see that quite clearly. So we saw a 69% slowing of brain atrophy. And we have data, since then, where we've dug into that, it's not just volume, but specific structures in the brain that are important for how the brain communicates within itself, and how it connects all this electrical activity. We've shown that it's actual structures that are being preserved, and that structural preservation in our hands always lines up with preservation of function.

NANCY LYNN: Interesting. So I guess somebody at the FDA was as astonished with those results, as I was, because you then received FDA breakthrough device designation. Can you just explain what that means?

BRENT VAUGHAN: Certainly. Device designation is granted by the FDA for products that are shown to have a breakthrough level of results in a disease that is not well-controlled or well-treated, that is a serious, chronic or even life threatening disease. And so they give it for serious indications for which there's a lot of unmet need, which means it's not being well addressed, for things that look quite unique, and have ability to really move the needle. So we submitted our Phase 2 data to the FDA. They granted us breakthrough designation for the treatment of Alzheimer's disease. And then what that means for us is that we were able to have more-- Thank you very much. --we're able to have more

accelerated discussions with the FDA that allowed us to design and start our Phase 3, our pivotal study faster, and gives us some avenues for quicker access to reimbursement and commercial once the product is approved by the FDA.

NANCY LYNN: Great. So Bert, let's go to the current study, the HOPE Study. And I will get us into that a little more gently. But Bert, on YouTube, wants to know how much time per day is it recommended for the patient to use the activated headset? Also wanted to ask from Belinda, do the visual frequencies, 40 hertz, have to be in sync with the audio frequencies, 40 hertz? Let me stop there, because I have a bunch more here. Let's do those. How many hours per day? So let me throw in. I'm sorry, Brent. Someone asked in the pre-submitted questions, must you have a care partner to participate in the trial. So if you could discuss that a little bit too, that'd be great.

BRENT VAUGHAN: Excellent So we do require folks to have a care partner. We enroll patients between the ages of 50 and 90, with mild or moderate Alzheimer's disease. They need to have a diagnosis, or at least we'll get a diagnosis as part of the enrollment, but a documented decline that aligns with Alzheimer's disease.

NANCY LYNN: Sorry, what does it mean? A care partner doesn't have to be your spouse, or your daughter, but who can qualify as a care partner?

BRENT VAUGHAN: There's a number of different folks that can qualify as a care partner. We very frequently see it as a spouse, that I think is probably the most common. Some people also have care partners that come into the home as part of care, and are usually in that home in a daily basis, but maybe not there all day. And so it has to be somebody who is able to be with the patient on a daily basis, and make sure that the patient is able to sit down and do the therapy, because to your other question, patients do this one hour a day. They usually do it as part of their morning routine every morning, and then they put the device on the charger and go about their day.

NANCY LYNN: And I will go back to Belinda's question about frequencies,

but someone else asked, and I just want to clarify, today, right now, this device is not available. You can only access it as part of the clinical trial, and then hopefully, if that clinical trial is successful, then people will be able to get this through their doctor, presumably, correct?

BRENT VAUGHAN: Correct. It is an investigational medical device right now, it is only available as part of the clinical study. If we are successful in completing the study, and then getting it approved, then our goal obviously, is to make it commercially available, and get it into the hands of as many patients and neurologists as possible.

NANCY LYNN: OK. And then Belinda is about frequencies. Did you want to address that? Do the visual and audio frequencies have to be the same or in sync?

BRENT VAUGHAN: The science gets a little complicated around that. We're doing a lot of science about how we match up, or alter, or think about the two different frequencies. And so each patient is part of the study. Remember, at the very beginning I said, the early science showed that they used EEG to see the difference between Alzheimer's and non-Alzheimer's patients. We actually connect those dots in part of our clinical study. We bring patients in, we get an EEG before they start, and then we are able to put the device on them in the clinic, and show that we can reestablish that brain activity and see it in the EEG before they send them home. And so each patient goes through that session, and that's part of how we set the device for them. So there is a little bit more complicated science about how we set up the device for each patient, so that they can get the optimal result.

NANCY LYNN: Brent, I'm just going to jump in, because one person, Sue, wrote in the chat, she said, when you go to the website, there's a form that you can't fill out. So is there a number people can call as well if they're having trouble with the site?

BRENT VAUGHAN: I will look into that to see why people aren't able to log in on the site, but I would say just check back to the site, and they should be able to get in there. Certainly when they go to the site, they can see all of the information that explains how do you get involved, and also what are the types of patients that are able to qualify for the study.

NANCY LYNN: And I was going to go do that next. So you have to have a diagnosis of mild to moderate Alzheimer's, be between 50 and 90, have a care partner. I also got from your website, you cannot have profound hearing loss. And somebody asked in the questions, what about vision loss? Will you be excluded if you have severe vision loss.

BRENT VAUGHAN: Probably. But there is a test. Everyone gets a vision test, and some form of a hearing test, and then we ultimately make sure that it works for them. What we found is that patients that come into the study, between eight or nine out of 10 patients actually are able to see the change in the EEG that says they qualify for the treatment. And so it's a fairly high number. But some people, it starts with a light and a sound. and being able to process those light and sound signals is how we start to drive the brain activity. If people can't process light, or they can't process sound, because they are deaf or blind, then it probably will not work for them, and they would not be able to get into the study. But there are degrees of vision impairment, and there are degrees of hearing impairment, and so that's why we screen each patient.

NANCY LYNN: I also have that you cannot live in a continuous care nursing facility, correct?

BRENT VAUGHAN: Correct.

NANCY LYNN: I have, you'll use the study device at home on a daily basis for about 12 months, it's eyeglasses and headphones. Let's see. And you will have some clinical visits with your health care professionals, and you will receive compensation for study-related expenses, such as travel and time. So I assume that if people get into the form, and they end up going through the process of seeing if they qualify, they will learn more about the compensation and the travel and so on. And again, how do they find, because I think this is just so hard for people, how do they find the site nearest to them? And somebody asked, what's the nearest site to Pensacola, Florida?

BRENT VAUGHAN: Actually, we have a lot of sites down in Florida.

NANCY LYNN: Yeah, Florida is usually a popular place.

BRENT VAUGHAN: It's usually pretty good. Once the site gets up and going, they can register their interest, and we'll be able to find them there. With 55 sites, it's a little hard for me to keep track of all of them.

NANCY LYNN: I assume there's no costs to the participants, somebody asked, is it covered by insurance. So I will assume there's no costs to the participants in the trial. When what would be the process, if this has a very positive outcome for people to understand whether or not it's covered by insurance?

BRENT VAUGHAN: Once we have data that allows us to submit at the end of our study-- so let me back up just a tiny bit. Our study is nearing full enrollment. And so in the next few months, we'll be enrolling our final patients. So we will make sure that we get resources back out to your people to find out the sites in their area. Once we're enrolled, it is a 12-month study, people are using this on a daily basis for 12 months. So about 12 months from now is when the study is looking to complete. Once we have the data from the study, if it supports approval with the FDA, then we will in turn submit for coverage with the various insurance companies and with Medicare. And so there is a path for us to ultimately gain coverage, like other medical devices. But we'll have to wait till we get there for that.

NANCY LYNN: So it sounds like we're two years potentially-ish away from it being on the market. So the way to get this treatment now, is to participate in the clinical study, so this HOPE Study, because it is recruiting its final members. And so if you have a loved one, or you have been diagnosed with mild to moderate Alzheimer's, this is the opportunity to do it. And how many more people are you enrolling, Brent, do you recall offhand, or roughly?

BRENT VAUGHAN: I don't recall offhand, but we have a few months of enrollment left. And so if people are interested, there is certainly time to get into the study. And to your other comment, yes, the only way that this therapy is available right now is part of the clinical study. We look to have that clinical study be done in just a little bit over a year. And then we will be engaging with the FDA, and trying to move towards commercial as fast as we can.

NANCY LYNN: That's great. So a couple of questions about other drugs. And one of your eligibility criteria is, says you must not have taken memantine, which is Namenda or Namzaric within the past 30 days. So we've had some questions about that, and also about whether or not you can take Kisunla or Leqembi after or concurrently. What are your restrictions to be in the trial?

BRENT VAUGHAN: Great questions. And the other drug which wasn't in there, which I'll go ahead and ask, because it'll be the next question we get, is about acetylcholinesterase inhibitors like Aricept. So patients that are on acetylcholinesterase inhibitors, like Aricept, as long as they're on stable therapy, and it's not changing, that is not a problem whatsoever for the study. And that's what we did in our Phase 2 study, and in our OVERTURE Study as well by the way. In our OVERTURE Study, we did not have any patients on memantine. And so for this study, we're making that a similar requirement. So if patients were on memantine, but they've come off for at least 30 days, they're eligible for the study, but we're not enrolling memantine patients right now. We do not have any experience. We're not enrolling patients that are on, either Leqembi or Kisunla at this time. Kisunla was only approved a number of weeks ago. In the future, that is certainly something that we'll explore. That's just not the scope of this study, because when we designed this study, neither one of those drugs had even been approved yet.

NANCY LYNN: And I'm not going to go into this in detail, we do have other episodes that go into the genetics of Alzheimer's in a lot of detail, and explain what the APOE4 protein is. And many of you may know it, but if you don't worry about it, because you would find it in your cognitive screening workup. But if people have two copies of the APOE4 gene, would they be able to participate. Is there any limitation on that genetic predisposition?

BRENT VAUGHAN: That's a great question. So we do do genotyping, so we will learn what copies of the APOE gene they have, whether there are four, four, or three, four, or three, three. But all of those patients are allowed into the study.

NANCY LYNN: Wonderful That's great. Roshana from Houston had written

in and asked, are the sound and lights being used adjusted for every patient, or the parameters are consistent for everybody?

BRENT VAUGHAN: We use that baseline session with the EEG to personalize those settings for patients. And then we send out the device that has been configured for them.

NANCY LYNN: I'm looking at the questions. Somebody asked if you have two copies, so you can participate if you-- What audio-free-- from Bert on YouTube. And I think Bert is very serious about this, because he's asking a lot of questions, so. Thank you, Bert. What audio frequency range is needed to function adequately in order to be accepted as a study participant? I don't know if you can say that offhand.

BRENT VAUGHAN: I can't. It's a little hard for us to actually explain that one. The easiest is, if that person qualifies for the study, they would be able to come in and actually have the functional test and see that if it works.

NANCY LYNN: And Brenda's asking, but it's a little confusing to me, because she says, from your clinical trial, Phase 2, it shows that the subjects that use the treatment for 18 months did better than the ones who received it for only 12 months. But I don't think that is accurate, unless I'm mistaken, I thought your Phase 2 study was six months. Or did you do an extension?

BRENT VAUGHAN: Our Phase 2 study was six months. At the end of it, we did do an extension, so we had patients that continued on therapy for up to 18 months. What we saw in that additional 12 months, is that the treatment effect for those who had been on the treatment arm seemed to persist all the way out to 18 months, which was great, which was great to see. And the patients who had been on the placebo/sham, for the first six months who had been declining, we had a slowing of rate of decline with them, both in terms of function, with the ADL measure, but also, in terms of brain atrophy or brain structural loss, as measured by the MRI. We saw that we slowed both of those similar to what we had seen in the treated group. But of course, we no longer had a placebo/sham to compare them to.

NANCY LYNN: And in the same vein of thinking about how much time, does it get a better effect, if you take it longer, or does the effect even out. There are several questions in the chat about, how did you determine that the one hour of treatment is the right dosage, let's say? Why one hour?

BRENT VAUGHAN: So that's quite complicated, because we saw that one hour worked quite well in the mice back in the original studies, and mice and humans are a little different, as I'm sure most people know.

NANCY LYNN: Very different.

BRENT VAUGHAN: And so in our other studies, we've looked at different doses, if you think about it. One hour has quite consistently worked for us, we do not think it's necessary to go longer than an hour. When we did some of our earlier studies, the one hour was quite well tolerated by patients. And we didn't have a safety or a side effect problem in an hour. And so that was the dose we used in our OVERTURE Study. And since it worked so well, and we're really looking to just repeat the treatment effect that we saw in the OVERTURE Study, but now doing it with more patients for a longer period of time, we've decided not to change that.

NANCY LYNN: I have two questions here that we really want to go get to, because they have to do with the terrible confusion that many neurologists and doctors have about trying to diagnose different dementias, including Alzheimer's and also their lack of understanding about clinical trials. And so let me read two of these, if I can quickly find the one that takes issue with neurologists. And I want to read it, because I share the pain. From Belinda on YouTube-- I have not met one neurologist who is aware, and if aware, discounts it, as it can't hurt, and I guess she means treatment options, I can't hurt to try. I am an early Alzheimer's patient with no dementia yet, and I have refused to take the drugs due to the side effects. Am I imagining a bias against any non-drug therapies. And I think this is a loaded question. I don't know if you want to answer it, Brent, but if you don't, I'll give my theory. But go ahead.

BRENT VAUGHAN: I'll give a short answer, and then I'll let you theory as well. I think really it's a lack of awareness. Our idea of using the Spectris device to use light and sound to treat Alzheimer's-- And this idea where

we started this whole discussion, instead of focusing on chemistry to try to change electrical activity in the brain, focusing on electrical activity that changes chemistry. This is a very novel idea. This was why, when we started doing this, it was quite novel. This is part of why we ended up getting a breakthrough designation in this space, because it was quite novel. And so for most neurologists, this is going to be a very new idea. It is certainly understandable and explainable to them. And we've seen many folks in the clinical community become quite supportive. And you talked about one of your advisors, Marwan Sabbagh, who does this, who's been really helpful in helping us think about navigating this. But besides finishing our HOPE Study, which is our pivotal study, there's a lot of education in front of us to educate neurologists. And I think that education for us will come in two forms. Number one, along with what Lilly is doing, what Biogen and Eisai are doing with their monoclonal antibodies, there is a lot of education for neurologists that there are new treatments coming down the path that can actually drive disease modification in the space, which has never been the case before. So step one is you can actually do things that will move the needle longer term here. And that's learning number one. Learning number two for us is, there are non-drug interventions coming down the path that can have a similar degree of effect. And so I would call this just more of, this is what happens when things are new, it takes a while for people to learn about them, especially if you have busy days seeing patients all the time. And that's an educational task for folks like us, like Lilly, and Biogen and Eisai.

NANCY LYNN: I agree that mostly it's lack of knowledge, and there's been several decades, really, when neurologists and doctors were not able to prescribe or advise patients to take anything, except Aricept or Namenda. And so there is a lack of understanding about the current anti-amyloid drugs, as well as potential new devices that are coming down the pike. And I do think that there is a bias. Let me not say that there's a bias against non-drug therapies, but this is my personal opinion, doesn't reflect on anything else, but it's a bias against something no one can make money on, yes. But people can make money on devices and technologies, and that's why there should not be any bias against this a technology, because somebody will make money from it. When you say, can I take coconut oil, which is not a proven help, but people are not going to pour millions and

millions of dollars into those studies, if they can't make money from them. So that is true.

This is another one about the unreliability, unfortunately, of our doctors. Rochelle-- I have been diagnosed with MCI, which the doctor said is the first step of Alzheimer's. But another doctor told me it isn't, which has me confused. Is MCI the same as mild Alzheimer's? That's a good question, and I hear this question all the time. And the doctors don't know how to tell people what they have. Sorry Brent, go on.

BRENT VAUGHAN: It seems like it should be such a simple question, but it's actually a very hard question. The MCI and Alzheimer's are different diagnoses. A large percentage of MCI patients will progress to Alzheimer's. And so it is often very hard. And when looking at, and speaking to the patient to tell what side of the line that they might be on. Historically, Alzheimer's has been defined as a type of dementia that is characterized by accumulation of amyloid plaque. And so in the early days, most definitive Alzheimer's diagnoses were made on autopsy, you could actually see the plaque. A few decades ago, they started getting better at doing PET scans. They were able to look at amyloid and see it in the PET scan. So now when doctors are diagnosing their doctor's office, advancing MCI and early Alzheimer's are very hard for them to tell apart. And so they are getting better at blood tests that are going to be able to help differentiate between the two. And that's an area that's moving really quickly.

NANCY LYNN: One thing we didn't really touch on is, what about if you were diagnosed with mild cognitive impairment, or will it work in other types of dementias? What if it's vascular dementia, or some other kind of dementia.

BRENT VAUGHAN: We're not doing studies in those populations right now. Those are areas of interest for us in the future. But right now, we're quite focused on trying to just move down the path with our first indication, which is Alzheimer's.

NANCY LYNN: But it could be tried for other dementias in the future.

BRENT VAUGHAN: We certainly hope so.

NANCY LYNN: I certainly hope so, too. And Ramona, your dog is adorable. Marlene writes in the chat, I was in the Lilly study with donanemab, which is now the market name is Kisunla, and finished the study in June of 2023. I had the infusions for 18 months, PET scans and MRIs at different times. Would I be eligible for this study. So if you were in one of those trials, are you are you eligible if you're not taking the drug any longer?

BRENT VAUGHAN: They're quite possibly eligible. I believe the current criteria is patients that had been on, and have a suitable washout period, which 18 months should be a suitable washout period, I believe that those patients will be eligible. And that's something we can follow up with. It's not a large number of patients, we have not seen very many of them, but we are trying to find ways to allow them into our study.

NANCY LYNN: So try, apply, and try to get in is what I would say. I think you mentioned this, but how long does someone have to be off of memantine to qualify, I think you said 30 days.

BRENT VAUGHAN: 30 days. And I did see a question in there about someone who said, if I discontinue memantine, could I get into the study. Obviously changing any medication you're on for the treatment of a disease, like Alzheimer's, is a discussion they should have with their physician. But if their physician decides that it makes sense for that patient to stop taking memantine, once they go through the 30 days, they would potentially be eligible.

NANCY LYNN: And I think I've seen two questions, this is from Ann. How about people with posterior cortical atrophy, will they qualify if they've had a diagnosis of mild Alzheimer's, or what can we say about that?

BRENT VAUGHAN: I'm sorry, could you repeat the question.

NANCY LYNN: How about people with posterior cortical atrophy, PCA?

BRENT VAUGHAN: So right now, not within the scope of the study. Once again, once we get through the study with Alzheimer's, there's a lot of

other areas that we think are quite interesting, related dementias that would make a lot of sense. But we're just not doing that study right now.

NANCY LYNN: And does the treatment from Brenda just slow the rate of the things we mentioned before, the loss of cognitive function, activities of daily living function, and brain volume, or does it help reverse it?

BRENT VAUGHAN: So right now, what we've seen is that it slows progression. We have not seen people that had loss function restored, but we have seen preservation of function, and preservation of brain volume. And we certainly believe, and I think most of the scientific community's believes, once patients lose this brain volume and brain structure through atrophy, there's not been anything that's been shown to restore it.

NANCY LYNN: And what's the difference between this therapy and TMS, transcranial magnetic stimulation.

BRENT VAUGHAN: So it's quite different. TMS stands for transcranial magnetic stimulation, and so they use powerful magnetic fields to try to induce changes in the brain. We do not do that. We do not try to use electrical or magnetic fields that we try to transmit through the skull into the brain. A lot of people find that a little creepy. That's not at all what we do, what we do is we use the way the body has developed over the years to process light and sound signals every time. Every time a light interacts with our eyes, it interacts with the retina, which then triggers the optic nerve, and that optic nerve sends a little electrical signal up to the brain. And so what we do is, we co-opt that. That same thing happens with sound when they interact with our ears. So we use these sensory networks of how we process inputs of light and sound, and those get translated into electrical activity, which is how the brain runs, right. The electricity is the fundamental currency of our brain. So we use the sensory networks to create activity in the brain. We do not use electrical or magnetic fields to try to modulate what the brain is doing.

NANCY LYNN: We're almost out of time. I can never believe how quickly these hours go by. I have two quick questions I want to ask. And if anybody has a burning question they want to get in, you can put your hand up, or just try to speak up. But Roshana had written, since you

were just talking about the light stimulation, what measures, if any are taken in consideration to use light stimulation, as almost 40% to 45% of Alzheimer's patients show epilepsy symptoms, which can be induced by bright and flashy lights.

BRENT VAUGHAN: So it's the frequency of the bright and flashing lights that are very important. We've seen a very, very small number of seizure-related episodes with all of the patients that we've looked at. And for those, oftentimes you can't tell if they have anything to do with the therapy. The frequency of our stimulation is in the low gamma frequency. Usually when people think about photoinduced seizures, when you think epilepsy, is an area where this comes up a lot, they usually are thinking about frequency rates that are down around 20 or lower hertz. We're greater than 2x times that. And so seizure-related incidence is something that we've not seen very much of at all. When they go through that EEG session, all patients, besides just seeing that we can get the induced activity in the EEG, it's a chance for every patient to make sure that it's well tolerated for them. And so that's something that we screen for before we enroll the patients into the study, and send them home with the device.

NANCY LYNN: My last question before I wrap up, my mother is 94 years old, so she doesn't qualify for your study, but she has mild cognitive impairment, she's probably watching us right now. If she were 10 years younger, what would you say to her if she was your mom and you were talking to her about this study? Just anything random, what would be the way you would convey to her, whether or not you think she should participate, what the benefits, what would you say, just anything that comes to your head.

BRENT VAUGHAN: Well my mom is in that bracket, she actually tried to get into one of the antibody studies. And she is a little claustrophobic. She was unable to sit through the PET scan to be able to be enrolled in that study. And so she was unable to get into one of the antibody studies. Unfortunately for her, she just was not able to get in our study either. But I would say, listen, if this is an area that you're eager, and helping to do two things, potentially have the ability to access an earlier treatment, which is what clinical studies do, but also interested in helping advance the

field, because ultimately what these clinical studies do is, this is how we ultimately get drugs approved and available for everyone. And so there's a chance to potentially help yourself, but also to help others. I think that if this is an area of interest, I just pasted into the chat for everyone, the link to the clintrials.gov site, and you can get more information about our study, and we can get you linked to whether or not there's a site in your area.

I think what's interesting about this is, that people have a lifestyle that allows them to be able to enroll in the study. To date, across multiple studies, we've seen no treatment limiting serious adverse events. When we talk to our clinical sites that are enrolling our studies, I have neurologists tell me every time I talk to them that this is one of their favorite studies to enroll, because when you enroll studies and you sit down with the patient and with their family, and you have to talk about the safety concerns of cerebral hemorrhage, or cerebral edema that comes with some of the other drugs in this space, we've seen no incident of that associated with our treatment at all. And so as one neurologist likes to tell me, the safety talk for the HOPE Study is the easiest safety talk I have. And so I think that for patients that are concerned about this, it gives them a chance to do something actively. And I think that for people in this group, which is my mother, I watch this impact. My grandmother, my mother's mother, and I watched her go from being so sharp to being just losing track of day to day, and the anxiety that goes with that. And so I think that all of us who have been around this understand the anxiety and stress of watching your peer group with this inexorable decline that they feel powerless over.

And so I think for folks who are interested, there is additional work involved in being in a clinical study. But people who are willing and have the ability to do this and want to do something active about the progression of this disease, as opposed to just waiting for a pill, or waiting for a shot, then this might be for you, and I encourage you to look into it. And if, for some reason it does not line up, because of geography, or where you are in disease progression, know that we're working on this to try to get it across the finish line as fast as we can.

NANCY LYNN: Brent, thank you so much for giving us such great and

clear answers today. And I hope that the study fills up as quickly as possible, so that we can get the results as quickly as possible. And really, really just want to tell you how much we appreciate your being here today.

And I'm going to ask Roger to bring up some of the closing slides. Here are some of the previous episodes. They're on our website at brightfocus.org/ZoomIn. And you can go to these to get the best expert information in pretty understandable language from these great experts. And go to the next slide, please. Here again is the link for the HOPE Study. And we're going to send all of this to everybody who's registered, and everybody who's participating. You will receive a copy of the recorded program via email, along with these links and these resources. All of the resources for all the episodes can be found at brightfocus.org/ZoomIn and on YouTube.

So one more slide. I did this slide a week or two ago, before something wonderful happened for BrightFocus. I wrote that, we are an organization who annually gives grants to two usually younger emerging scientists. And I wanted to tell everybody that we had just gotten approval to give 25 new research grants this year as an investment of more than $6 million. But in the last week and a half, we received some fabulous news. We are receiving a grant from an anonymous foundation of $3.2 million that will allow us to fund 12 additional grants that were approved by our Scientific Review Committee, but we didn't have enough money to fund. So that's 12 more researchers who will be in the field for maybe 40 years. So I'm very excited, I'm saying that's 500 years of research that this grant has funded. So I just wanted to share that with you all, because as we heard from Brent, this is without the slightest doubt, the most exciting time in Alzheimer's research that we've ever had. And the fact that there are studies like this that show promise and are encouraging seems miraculous after many years of nothing quite working.

BRENT VAUGHAN: And Nancy, if I could just pipe in for just a second there. I've been working in the Alzheimer's space-- I was doing this 20 years ago when I was working with Novel Drugs and Alzheimer's. And just for all the folks on this, in the last 13 months, we've seen the approval of Leqembi. July last year, we just saw the approval of Kisunla. These are

the first two disease-modifying therapies for Alzheimer's ever. These are the first two drugs approved in this space in over 20 years. And here we see two of them within 12 months, and other things coming down the pike. If there ever there was a time for hope in Alzheimer's, this is why we named our pivotal study HOPE. But if ever there was a time for hope in Alzheimer's, it's right now, it is truly one of the most exciting times to be looking at progress in this field.

NANCY LYNN: And I know we're over time, but it's a tough time, because it's the most exciting, most positive time. And then we haven't really educated the doctors and the neurologists enough to bring the public, along with us, and that's part of why we're doing these series. So if you have suggestions for future topics, you can email us at reply@brightfocus.org. If your questions weren't answered, you can try and send them here, and if we can answer them, we will. And last slide, Roger. Here are our upcoming episodes. The next regular episode of Zoom In on Dementia and Alzheimer's will be Thursday, September 19. We expect that may be changed to the next Thursday after, we will let everybody know. And then on Thursday, October 3, we have the next Zoom In on Dementia and Alzheimer's Clinical Research. So you can take the slides down now, Roger. Thank you so much for helping, and Alexa and Dr. Rossi. And thank you all for participating. I hope this has been informative and helpful to you all. And really appreciate everybody's time, especially yours. Brent, Thank you so much.

BRENT VAUGHAN: Thank you so much, everyone.

Resources

BrightFocus Foundation: (800) 437-2423 or visit us at BrightFocus.org. Available resources include—

- The HOPE Study
    - https://www.hopestudyforad.com/
    - https://clinicaltrials.gov/study/NCT05637801
- The Stages of Alzheimer's – How Does Dementia Really Progress?
    - https://www.brightfocus.org/alzheimers/zoom-dementia-alzheimers/stages-alzheimers-how-does-dementia-really-progress