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

The New Alzheimer's Drug: What is Leqembi?
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Transcript of Zoom with Sharon Cohen, MD, FRCPC, Medical Director, Toronto Memory Program, and Behavioral Neurologist

NANCY LYNN: Welcome. This is the first episode of Zoom in on Dementia and Alzheimer's, a new monthly ask the expert series brought to you by the Alzheimer's Disease Research program with generous support from educational grants, from Eli Lilly and Company and Genentech. Thank you so much for joining us.

My name is Nancy Lynn, and we are very fortunate to have for this first episode Dr. Sharon Cohen, sharing with us and answering your questions today about the new Alzheimer's drug, lecanemab, which is being marketed under the name Leqembi. And first we're going to put up a slide just to do a little bit of housekeeping that hopefully helps us all. The program is being recorded and live-streamed. The recording will be emailed to everyone on this call after it's edited and finished. I really want to encourage everyone to ask questions. You can do this two ways. You can type your questions into the chat box, or you can use. You can ask, live by using the raise hand feature. To use the raise hand feature, you will bring your cursor to the bottom of the screen and over to the right. You're going to see a little kind of a smiley face that says "reactions". And to raise your hand, I'm going to do it, you click the reactions button and all, across

the bottom, you're going to see a bar that has a little hand raised, and it says, "Raise hand" and that's what it looks like. And that way we'll know that you want to ask a question live and we can hear your voice, and you'll be unmuted to do that. We received about 150 pre-submitted questions, so we know that a lot of people have a lot to ask about this drug. So I'm just going to note that personal questions cannot be addressed directly. So, if you do have a personal question, and can make it kind of general, that would be helpful. So I think we'll just get started. Dr. Cohen and I met about a month ago to start our conversation and we pre-recorded some questions and answers to get us started. So we're going to play this 7 minute video and you can start typing questions in or you could just listen, and then we'll do Q&A after that. So, let's go ahead with the video.

NANCY LYNN: Well, we are just delighted to have Dr. Sharon Cohen here with us today. Dr. Cohen is a behavioral neurologist and medical director and site principal investigator at the Toronto Memory Program, which is a community based medical facility specializing in the diagnosis and treatment of Alzheimer's disease and related disorders. And the Toronto Memory Program has one of the largest clinical trial programs for Alzheimer's disease in Canada. Did I leave anything out Dr. Cohen?

DR. SHARON COHEN: Perfect. Thank you so much. Pleasure being with you.

NANCY LYNN: Thank you so much. Well, we're recording this in March, and there's all such a flurry of news that there is a new Alzheimer's drug. So, for people who aren't in the field, and can't quite follow what's going on, what is this new drug for Alzheimer's?

DR. SHARON COHEN: Yes, it's an exciting time. There is a new drug, as of January 6th, the FDA gave conditional approval to a drug called lecanemab, and the brand name is Leqembi. Might be easier for some people to pronounce, Leqembi. And this is an antibody that clears amyloid and gets at one of the root causes or what are the bad proteins in Alzheimer's disease. So very exciting times.

NANCY LYNN: Is it a tablet? How do you take the drug? What kind of drug is it?

DR. SHARON COHEN: We give it by an intravenous infusion, and the intravenous infusion is actually given every 2 weeks. So it's quite a commitment to take this drug, and very different from the Alzheimer's drugs that we've had in the past, which were pills.

NANCY LYNN: I guess I know there are other differences with this drug as well. So what does this drug do? I understand that the clinical trial that tested Leqembi in 1,800 people, the drugs slowed down the pace of the progression of the person's cognitive loss by about 27% over those 18 months. So, according to the scientists, this means it would take someone on the drug about 7 months longer to reach the cognitive loss level of someone not on the drug and we're still exploring that. But also improves the functions for activities of daily living. What does that...how does that manifest?

DR. SHARON COHEN: So in Alzheimer's disease, not only do we lose memory and other cognitive abilities gradually, but we also lose our ability to be independent in day-to-day functioning, and if we can slow down the loss of independence, which is what Leqembi can do, not just you know slow down the loss of memory on a cognitive test, but also slow down the process of losing one's activities of daily living so that one can stay independent longer. And if you treat at an early stage of disease, when people are still relatively independent, living in the community contributing to family life and society, that's the ideal stage to slow this down.

NANCY LYNN: Is the drug available now? Can people get it now?

DR. SHARON COHEN: It is available, and the cost is not yet covered through Medicare. So that is a major obstacle for many. Most seniors rely on public funding. And we are hoping to have full, unconditional approval by the summer of this year.

NANCY LYNN: You already mentioned that Medicare has not made a decision to cover the drug, so if at this stage, if somebody wants to get on the drug, do we have any sense of what it will cost?

DR. SHARON COHEN: So what I understand is that the drug itself would be $26,500 USD per year. And then scans. PET scans can cost a few

thousand dollars, variable, depending on the center you get them from. A spinal tap is another way to determine that one has amyloid in the brain by analyzing the spinal fluid. This is a much less expensive procedure, and it's a very good one. It's just as accurate as a PET scan of the brain. Some people shy away from the spinal tap as being invasive, but having, you know, seen many, many patients at our clinic have a spinal tap, I can tell you it's very well tolerated, and it's a very good less expensive way of having amyloid confirmation, and that is available in the US.

NANCY LYNN: Who will be eligible to take this drug?

DR. SHARON COHEN: So it's at the mild cognitive impairment stage, and the mild dementia stage that Leqembi is indicated. And so very important that we don't let our patients miss a treatment opportunity. We don't want them to spin their wheels and try to get attention over many years, and the disease progresses and then it's too late for them. We really have to listen to people, you know. If somebody tells me their memory's not right, it's up to me then to explore this, and not just sort of pass it off and what do you expect for being 70 or something like that.

NANCY LYNN: And there's been a lot of publicity about side effects. So can you give a basic description of what side effects may come along with this medication?

DR. SHARON COHEN: Sure, I'm happy to say that for the most part the drug is well tolerated. Some individuals, perhaps a quarter of individuals on Leqembi will have an infusion reaction, generally with the first drug administration. They may have chills or feel unwell for a few hours. So infusion reaction would be the commonest side effect in those who are going to develop side effects. The second group of side effects are something called ARIA, amyloid-related imaging abnormality. That's a real mouthful. But imaging abnormality, what that suggests is this is a side effect that we see on MRI imaging. So on a scan. It's usually not something that causes symptoms, but it can. And we need to monitor for it and ARIA can take 2 forms. It can take the form of some swelling in the brain. Usually temporary, mild to moderate, goes away on its own without any treatment, but we might want to hold the dose while people have that swelling. And there's another type of ARIA, other than the swelling, and

that's little spots of bleeding. And that sounds very scary, but often these little spots of bleeding, we call them microbleeds or microhemorrhages. They don't cause any symptoms at all. None the less, we want to monitor for this, and make sure that we're not getting more and more of these. And if anybody is symptomatic, maybe dizziness or any other symptoms, headache, then we would hold the dose of medication, monitor until the ARIA clears on MRI or stabilizes before we resume dosing. ARIA shouldn't be a deal breaker here, because it's generally manageable, usually mild, transient. So it's something the physician needs to discuss with each patient.

NANCY LYNN: Thank you so much for being with us and now we're going to open up the program for Q&A. Thank you, Dr. Cohen.

DR. SHARON COHEN: Such a pleasure. Thank you.

NANCY LYNN: And here she is in person. Dr. Cohen thanks so much for being with us. I would imagine there are a few people with questions. So please again, I'll repeat, if you would like to ask a question live, please raise your hand, use the raise the hand, under reactions at the bottom of your slide, and then we'll get to some that we're in the chat, and some that were pre submitted as well. Why don't we start with Michael? Nice to see you, Michael.

MICHAEL: Nice to see you. Thanks so much for having this program. There seems to be a lot of chatter coming out in the last week or so that this group of drugs that they recently have identified for dementia is also creating a brain shrinkage. Is that true that you're aware of? And what is the consequences of that brain shrinkage? Is it actually creating a problem that we are actually losing more memory because of it?

DR. SHARON COHEN: I'm happy to answer that. Yes, thank you, Michael, for the question, and you're right. There has been a bit of a buzz about that, so it's good for us to get our facts straight. So in general, when the brain shrinks, because brain cells are lost, that's not a good thing. And we know that millions of brain cells gradually die in the course of Alzheimer's and the brain shrinks. So that kind of reduced volume, we don't want that. With drugs antibodies that target amyloid and clear amyloid plaque from the brain it has been a characteristic finding that, despite benefit to

cognition, to daily function, to all the clinical measures, there seems to be some reduction in brain volume. And so we are trying to understand is this because a certain volume of plaque is now removed and that's what the reduced volume is? Is it because the inflammation in the brain, you know all the inflammatory cells and other inflammation products are now reduced? Is that why we have this MRI finding of reduced volume? So many of us do not think this is really atrophy or shrinkage of the brain. It's getting rid of some of the elements that injure the brain. I think the jury's out. We have to, you know, sort of take a longer scientific perspective on what this means. I've heard people call this pseudo atrophy, really reluctant to say this is the true atrophy of brain cell loss. We don't think that's what it is, so I hope I hope that helps.

NANCY LYNN: Thank you, Michael and Mark? Can we unmute Mark please, Mark. C? Mark, and maybe you can unmute yourself too. There, almost.

MARK: Okay, I'll come off mute. Now, can you? Okay, now, you're okay.

NANCY LYNN: Great.

MARK: I guess I want you to allay my skepticism. When I saw the report, it was it, it slowed things down by maybe 37%. Since we don't know what any individual's progression would be, how can we be saying this slowed it down?

DR. SHARON COHEN: Okay. Sure, that's a fair question. So when we do controlled trials, we have a placebo treated group. So people who aren't actually getting the lecanamab, and we have the actively treated group, and they are well matched. And this was a large phase 3 study that we're talking about, the Leqembi, lecanemab, results from. So we had a large population being studied, well matched in terms of age, stage of disease, background medical conditions, background medications, other factors. And we compared the rate of decline over a period of 18 months in the trial for those who were not treated with lecanemab compared to those who were treated. And that's how, based on these 2 groups, treated and untreated, we can say without any reservation, it was very statistically significant. There was a slowing of cognitive decline in the Leqembi treated group compared with the placebo control group of 27% less

decline on cognitive measures, 37% less decline on day-to-day functional measures. Now you're right, Mark that for any given person, we don't know if your fast progressor or slow progressor, but based on the Phase 3 trial data, we would expect that someone's going to have a slower progression of their disease on treatment with lecanemab then not on treatment. I hope that helps.

MARK: Yeah, and so you're actually slowing it. You're saying it, cause I had heard that got rid of a lot of the amyloid, and that. But they're also saying, not only did it get rid of the amyloid, it did in fact, slow the progression.

DR. SHARON COHEN: Yeah, and that's very important. Because, you know, I mean, that's exciting to clear amyloid. But we don't want to just treat a scan. We want to treat people's symptoms and know that they're functioning better. So yes, very consistent results with the lecanemab data that not only do we substantially remove amyloid, but we slow cognitive decline, we slow functional decline, and we maintain people at a more independent level with better quality of life for a longer period of time. So all of those outcomes are really important. If we just cleared amyloid, but people didn't do any better because of it, then that wouldn't be a successful drug.

MARK: Thank you.

NANCY LYNN: Thank you, Mark. Let's go to Lenora.

LENORA: Thank you, Nancy and Dr. Cohen, for hosting this forum. We mentioned, or you mentioned, that the FDA approved the product in January, with some restriction for it to be covered by Medicare. It's necessary for a patient to be in a clinical trial. So, if there's no clinical trial available, in a patient's area, what can we do? What can, what can be done to get their hands on this product, to get their hands on the drug?

DR. SHARON COHEN: Well, thank you, Lenora. You are raising a very important question. So the FDA in January of 2023 did grant conditional approval for lecanemab, based on Phase 2 data, for lecanemab, that showed that there was very substantial lowering of amyloid which was likely to predict better clinical outcomes, so less loss of memory and less

loss of daily function. The Phase 3 data is now being reviewed by the FDA, and this is confirmatory data to show, you know, beyond any doubt, that lecanemab does more than, as we were discussing with Mark, more than just clear amyloid yes, absolutely people do better on this drug in terms of day-to-day function. And the FDA will render a decision as to whether to convert their conditional approval to full traditional approval in July, on July 6, 2023. What we hope is at that point the centers for Medicare and Medicaid will fully cover the cost, because the FDA, if they're saying this drug is safe and effective, we don't think that CMS should say, you know that the drug should not be covered. So right now, there's quite a bit of activity trying to, you know, educate and advocate to cover lecanemab even at the stage of conditional approval. And I do support that, and I think that Nancy will talk later to you know the ways we can all help advocate, but we're hoping that the cost coverage issue will become a much better addressed in July, should we have FDA full approval.

LENORA: Is there any chance, though, that if they don't, or even if they do, and a clinical trial isn't available, isn't close enough to a patient, that there that the geriatricians, neurologists, where else can they possibly go to get availability to the product?

DR. SHARON COHEN: Yeah. It's a very difficult situation not to have cost coverage, because the participation in a CMS clinical trial is not something that is even established, and there isn't a lecanemab ongoing trial for people with mild cognitive impairment and mild Alzheimer's disease. That data is already submitted. So there are other lecanemab studies in prevention, but that's a different matter, and maybe we'll discuss that later on. So there isn't even you know, even if you're in a you know, an academic, urban location, you can't necessarily access lecanemab through a CMS trial. That's sort of a hypothetical construct right now, that trial doesn't exist. So it's a little bit infuriating, more than a little bit, and don't have a good answer. It's not a matter of traveling somewhere at this point.

LENORA: Okay, so the doctors don't have access to it. And you said that there's scans necessary. So it's a bigger process than maybe to the average doc just doesn't have access to.

DR. SHARON COHEN: Right, so physicians would be authorized to prescribe the drug, but the cost would not be covered. So the FDA

approves a drug, there's a biologic license, the prescribing physician can give you a prescription could have an infusion center setup and the means to deliver the drug. But the cost is the barrier for most Americans.

LENORA: Yeah. Very frustrating.

NANCY LYNN: So just to clarify Dr. Cohen. The drug is available. If you go to your doctor outside of a clinical trial, it just is not covered, and it's expensive.

DR. SHARON COHEN: Yes.

NANCY LYNN: That's just to make sure that's a clarification. Let's go to Janet B. And then I do have a question from Vimeo as well. Let's go to Janet.

JANET: Thank you. My question has to do with the AHEAD study or other studies that are looking at this drug for prevention purposes. Can you speak to what the data is behind that so far? And maybe just speak generally to that study for prevention.

DR. SHARON COHEN: Sure. Thank you, Janet. That's a great segue from our previous discussion. So in the last several years, in Alzheimer's drug development, we have understood that it's important to go earlier in the disease, because, as I said at the beginning, so many brain cells are lost in this disease. If you apply treatment too late, it's hard to play catch up. It's like treating metastatic cancer. Not to say we should ignore our citizens who have severe disease; we need other treatments. But to slow disease at an early phase is where the actions at. Now we have the lecanemab Phase 3 data that I talked about that provides evidence that the drug is safe and effective in people with mild cognitive impairment due to Alzheimer's and mild dementia. The AHEAD study, is going even earlier, and it's saying, well, what about people who are cognitively normal, but are at risk for Alzheimer's? And let's say, in screening for it AHEAD, we do a PET scan, and amyloid is already building up. Why do we have to wait until people develop mild cognitive impairment or dementia from Alzheimer's? Can't we do something early? And it might be that's the best stage to tackle this disease at. So the AHEAD study is designed for people who are

at risk for Alzheimer's, either by virtue of age over 65, or they have a copy of the APOE4 risk gene, or they have a family member with Alzheimer's, so they could go down to age 55 if they have this additional risk factor, and are still cognitively normal. They may have some symptoms. They may feel their memory's not as good as it was a few years ago, but on cognitive testing they are still normal. They would get a PET scan, screening for the study, and if amyloid's accumulating they could go on to treatment with lecanemab within the controlled trial, and that trial is very actively ongoing in many centers, including ours in Toronto, and people are excited, you know. Let's act early. We won't have the results of the trial for a few years. So if the trial's successful, if we can slow down or delay people moving on to symptomatic phases of the disease, then we will have a prevention indication. But we don't have that yet.

JANET: What is the PET scan threshold for qualifying?

DR. SHARON COHEN: Sure. So that's interesting. So when you get a usual PET amyloid scan, the FDA criteria that it's read as amyloid positive or amyloid negative. And it usually takes about 30 centiloids or more, so centiloid is the unit of amyloid plaque accumulation for a PET scan to turn positive. However, in the AHEAD study, it's very cleverly designed. They're looking at people who are at the 30 and above, but also an intermediated or subthreshold amount of amyloid, with the understanding that you know, maybe you don't have really a full brain of amyloid, but you're on that trajectory, and shouldn't we also consider those people who are not quite amyloid positive by the usual FDA determination, but may get there in the next few years. So we're looking at people who are even under the 30 centiloids of amyloid.

JANET: One short follow-up. What does it mean if somebody is not even in that intermediate level?

DR. SHARON COHEN: Yes, so that is on the one hand, good news, you know. If you're cognitively normal, you may have risk factors for Alzheimer's but there's absolutely no evidence of amyloid in the brain, then you do not have Alzheimer's. Will you develop amyloid plaque in the next few years? Maybe. You know, we don't have guidelines yet on should you have a repeat scan in a year or 5 years? Or you know the way we have

with colonoscopy or mammography, how often you should screen if you're at risk. But it's good news in the sense that there's no Alzheimer's, there's no sign of Alzheimer's. You wouldn't go on any further in the AHEAD study, and you wouldn't do anything further from an Alzheimer's perspective at that time. However, if somebody has subtle symptoms, even if they are cognitively normal, they still deserve a thorough investigation as to what else this might be, because not all memory loss is Alzheimer's. So the PET scan gives a clear confirmation. Yes or no, for Alzheimer's changes in the brain. But then there might be some follow-up that needs to be done.

JANET: Thank you.

DR. SHARON COHEN: You're welcome.

NANCY LYNN: Thanks, Janet. There's a question that's come in from someone watching on Vimeo. Can it gain back function, or does it just slow the loss of progression?

DR. SHARON COHEN: Yeah, that's a great question. And what we would love is medications that can reverse, you know, cognitive loss and functional loss as well as slow down the disease. For lecanemab, right now the evidence is that it slows down the disease. It doesn't reverse things that are lost. However, let me say this, if a disease is moving very slowly, it gives you more chance to compensate, to learn strategies, to function better. So it is possible for people to do better, even if that's not the biologic mechanism of the disease. So the slower a disease moves, the more you can cope with it and have work arounds.

NANCY LYNN: And I'm going to tag on to that here for someone named Jolene, surprisingly, in the chat. Am I correct in understanding that treatment helped for up to 7 months? So can we clarify that 7 months was just within the framework of the 18-month trial, and what we don't know what we'll happen in, the longer, the longer term application?

DR. SHARON COHEN: Right exactly. And so just to expand on that and thank you, Jolene, whichever Jolene you are, for the question. What

we saw with just about all of these clinical outcomes, whether it was cognition, memory testing, day-to-day function, quality of life, what we saw is a significant change starting around 6 months. There was a separation between those treated with lecanemab and those on placebo. So there's already slowing of disease at 6 months, and the magnitude of difference between those 2 groups increased over time. So if you can sort of think of a graph where the lines are diverging, not just staying parallel. So there's a difference at 6 months, greater difference at 12 months, and by 18 months, which was the duration of the trial, the separation was even greater. So at 18 months we saw with day-to-day function 37% less decline. If those trajectories continue out to 2 years, 3 years, that percentage of slowing, you know, could be 50%. It could be more than that. So the 7 months saving is sort of a snapshot in time. It doesn't really allow for the modeling that we are getting greater benefit the longer you're on the drug. And so we don't actually know what the maximum benefit will be. We will learn that by following people in clinical practice, and by what we call the open label extension of the Phase 3 and the Phase 2 study that are still ongoing.

NANCY LYNN: And before we come back to you, Michael, there were several questions submitted ahead of time, saying, what is the difference between Leqembi and Donanemab? Which is another drug that may get some, get approval soon. And so I'm going to ask, on behalf of the many people who asked about that, what's the what's different about Donanemab and lecanemab? And are there other drugs that we should be expecting to be approved in the relatively near term?

DR. SHARON COHEN: Okay, so this is a brainy audience here. So donanemab and lecanemab belong to the same class. A class of antibodies that target amyloid. Within that class, the individual drugs of which lecanemab and donanemab are 2 of several, the individual antibodies are all a little bit different. They differ in what aspect of amyloid they target and clear, how fast they do it, their safety profile, you know, the rate of side effects. So we don't want to think of this class as all the same. Now, if we look at lecanemab, this is an antibody that recognizes and is highly selective for a soluble form of amyloid. And many people would feel that the soluble aggregates of amyloid are the most injurious to the brain, the most damaging. Donanemab is very specific in targeting plaque, insoluble sort of late developing amyloid, amyloid goes through

a success of metabolism, from soluble small to larger aggregates, to insoluble plaque. Donanemab targets plaque. Now does it matter? They both clear amyloid on a PET scan, because on a PET scan we are looking at plaque, but lecanemab also clears soluble amyloid. That may be very important. We'll see what the donanemab Phase 3 data show us. Is it comparable? Is it different? And does it have something to do with the different targets of these antibodies?

Another way, and I won't go on too long, because I know there are other questions, but donanemab requires some dose titration. I'm not saying that's a good or a bad thing, but with lecanemab, the starting dose that you receive intravenously is the optimal dose. So there's no titration. So you're not losing any time getting to the best dose. With donanemab, it's not a long titration, and the drugs given once a month. So that's more convenient than every 2 weeks, but it does take a few months to get to the target dose, and on and on there are other differences. But I won't, I won't belabor it.

NANCY LYNN: Thank you. Michael?

MICHAEL: Yeah, I have a 2-part question. The first part is, I know you're focusing on the amyloid with this trial of drugs. But have you seen or heard any change from the tau perspective in combination?

DR. SHARON COHEN: Yup, yeah, that's great. So not only does the anti-amyloid antibody lecanemab, but we've seen it with donanemab and aducanumab, not only does it robustly clear amyloid, but it has a downstream effect on the tau protein. So tau is another bad actor in Alzheimer's disease. It's a protein in the brain that gets misfolded and injures brain cells. And by drawing amyloid out of the brain that seems to normalize tau, even though the antibody doesn't target tau directly. We have had multiple drug development programs with drugs targeting tau specifically, and to date, those have not had as much success lowering tau as the anti-amyloid. And that sort of supports the idea that amyloid comes first in Alzheimer's. It rises to a certain threshold. It triggers tau to become abnormal, and if you can deal with amyloid, you can also quiet down tau. In the end, Michael, we will probably have better ways of targeting tau then we've had so far, and they'll probably be a cocktail of therapies,

or depending when we catch one's Alzheimer's, maybe it's amyloid treatment, maybe you need a combination, or maybe at a certain stage we go directly with a tau therapy. And there are other mechanisms also being targeted. So it's complicated disease. But yes, we are seeing improvement with tau. Another thing with lecanemab, that we're seeing, is that markers of inflammation are improved. So again, this is really giving us biological evidence that the drug is doing something substantial to the underlying brain, changes.

MICHAEL: Great! That's fabulous. I haven't heard that, and I think that's fantastic news. I think they should talk more about that. The second part of my question is, you mentioned a brain study. In that are they taking people who fall under SNAP? I don't know if you're familiar with that terminology. I learned about it I guess about 4 or 5 years ago, SNAP, I don't remember what it stands for, though, but it's for people who have don't have the amyloid, but they still fall under the possibility of having some type of dementia.

DR. SHARON COHEN: Right. So there are lots of Alzheimer's lookalikes and SNAP sort of refers to these non-Alzheimer's lookalikes. And you know, what do we sometimes confuse with Alzheimer's? Well, it could be Lewy Body disease, frontotemporal degeneration, a whole host of other diseases that can look like Alzheimer's. And if we don't do a PET scan or a spinal tap to check if amyloid's there, then we could be very mistaken. Now a drug like lecanemab is very specific for Alzheimer's. In a disease like Lewy Body disease, there's a different protein. It's called α-SA nucleate. And we would need to target α-SA nucleate in the specific pathology. So yeah, it'd be great to have a drug that helps, no matter what the cause of dementia. We're really not there yet. But what I'm hopeful, very excited about is, what we've learned with Alzheimer's drug development will have carry over for other dementia's, in that number one, people looking at Parkinson's disease dementia, or Lewy Body dementia, frontotemporal dementia, they are understanding they have to go earlier in the disease, and they need a marker, a biologic marker, to make sure they have the right patient population. And then targeted therapy can have a chance to be successful.

NANCY LYNN: And thanks. Michael. I'm going to ask something, also, several people asked, and this is a tough one. So sorry, Dr. Cohen, about this, but many people asked about the other drugs that have been on the market for a while. And are they really effective? And how are they different? Ultimately there are many, many questions about this. Should I be taking those drugs? Do they really do anything? Does this really do anything? And I think it was summed up by somebody who wrote essentially, do these drugs just delay the inevitable? So how would how do you respond to your patients when they come with this line of questioning?

DR. SHARON COHEN: Thanks, Nancy. We've had drugs on the market for about 25 years. Starting with donepezil, tacrine before that, donepezil which is commonly referred to as Aricept®, rivastigmine, galantamine. These drugs work on downstream chemicals in the brain. What do I mean by that? I mean when brain cells are dying, they are not producing the chemicals that they need to support brain cell function. And so, you know, back in the, you know, 2000s or 1990s we were looking at can we prolong the action of these chemicals. And the main one acetylcholine, some of you will recognize that name. So what the class of cholinesterase inhibitors, sorry to throw in the jargon, what these drugs do is boost the amount of acetylcholine. But unfortunately, that's a little bit late in the disease. The drugs are not indicated for the mild cognitive impairment stage. So you already have dementia, and the impact is modest. So some people do get a boost in memory, and thinking, they feel sharper, they feel that they're more themselves. That is great. We don't want to minimize any benefit that somebody gets, but it is not a dramatic improvement that we generally see, and some people will not get any benefit. So it's very difficult to predict who's going to benefit. Unless there are contraindications, and there rarely are, I always offer my patients the option to try something. Let's see if we can boost memory and thinking. I tell them what the side effects might be. It's a once-a-day medicine. You don't need expensive scans. You don't need to have a PET scan ahead to confirm a diagnosis. If we think this is Alzheimer's, let's try it. And we will know within, you know, a few weeks to 3 months, whether it's helpful. And if it's helpful I would stay on it. If it's not helpful, then the option is just to stop it. So that's where we've been for the last 20 years. Modest

symptom benefit, not getting at the underlying major drivers of the disease early on, and not being able to really slow down the disease. So does it prolong the inevitable? Well, I think if it helps people, you know, do better for a time, that's worthwhile. But no, it doesn't slow down the accumulation of amyloid or tau, or inflammation in the brain.

NANCY LYNN: Thank you. Somebody mentioned in the chat here, not being able to participate in a clinical trial, because their blood test did not show traces of amyloid. So I actually thought I would just mention, because this is the other, besides this being the first time, there are potentially disease modifying drugs on the market. The other huge breakthrough in our field is that in addition to the PET scans, and you mentioned in the pre-recording the spinal tap, there are now seem to be blood tests that can detect these proteins, the amyloid protein, the tau protein in the blood, which would mean that certain dementias could be diagnosed with the blood test instead of these more expensive and invasive tests, quickly, less expensively. So the question in the chat was, how reliable are those tests? And the second question, which is a good one, is, if I don't have the amyloid does that guarantee that I'm not going to get Alzheimer's?

DR. SHARON COHEN: Great. So, the gold standard for confirming Alzheimer's changes in the brain currently is still a spinal tap, looking at the spinal fluid, or a PET scan, PET amyloid scan. However, blood tests are important. They are under very careful and fairly rapid development. There is, there are 2 blood tests that have been on the market for a little while in the US - Precivity or C2N Diagnostics has blood tests. But there will be more coming. Right now, most of the experts feel these blood tests are prescreening blood tests. They are not diagnostic tests. So if I have a blood test for tau or for amyloid, and the result is negative, then what that means is, I am not very likely to have amyloid on a confirmatory test, on a PET scan for example. But it's not quite as accurate as actually having the PET scan. So will the accuracy improve enough that these would be standalone diagnostic tests, or will they always be screening tests to see who should move on to a confirmatory test? I think we'll have to wait, not too long, but maybe another year or 2 for that answer.

NANCY LYNN: Thank you so much. I think we have time for one or 2 more questions. So if you're holding back now's the time to raise your hand. But I'll ask in the meantime another of the pre-submitted questions. You have mentioned that right now the drug is indicated for people who have a diagnosis of mild Alzheimer's disease. Do we know whether people are going to be able to take it if they are further progressed? If they are further along?

DR. SHARON COHEN: Right now the FDA label or the indication is for 2 stages of Alzheimer's. One is called the mild cognitive impairment stage, and just to be clear, this is where there's a memory problem. We see it on the cognitive testing. So testing is not normal for that person, for their age or education, but they're still functioning independently. Maybe you know, exerting more effort to get things done or relying on lists more, but still independent. That's the mild cognitive impairment phase of Alzheimer's. And the mild dementia stage, which is the other stage that lecanemab is indicating for is the mild dementia phase where people have lost some independent function. Maybe they cannot drive, maybe they're not banking. They've given up a few things they used to do, but they're able to do many other things. So that you know, sort of in broad strokes is the mild stage. We don't have evidence yet that lecanemab helps in more moderate stages of Alzheimer's or severe stages. And the study underway that we've mentioned a couple of times, the AHEAD study, is looking at even earlier for prevention in cognitively normally. So right now we have this window, that encompasses mild cognitive impairment and mild dementia due to Alzheimer's disease, and I think that prescribing physicians would be unlikely to air beyond those boundaries, because the evidence isn't there yet that it is helpful or safe.

NANCY LYNN: Thank you. I think this will likely be the last question. It says Jolene has her hand raised. I know you're not, Jolene, but hang on one second while we get you unmuted. Alright!

JOLENE: Yes, I have not been keeping abreast of more recent findings, but I do remember about a nun living in a religious community, and for some reason I remember the autopsy results showed that she had tons of amyloid, and there was no sign of any cognitive dimension at all. And

I'm just wondering is tau more indicative of Alzheimer's disease and has this happened again? Was this just a fluke, or is there some other basis for Alzheimer's, you know, being in progression or being in progress, you know, regardless of amyloid? I don't know. Yeah. I'm confused about the why everything is amyloid, amyloid. And yet this case happened.

DR. SHARON COHEN: Yes, yes, thank you. So let me try and set this stage here by saying that amyloid starts accumulating in the brain in people who are destined to develop Alzheimer's, 15 to 20 years before symptoms so it is possible to have a head full of amyloid on a PET scan, or to have evidence of amyloid in the brain on spinal fluid, without symptoms, and so that person wouldn't have been, you know, in previous clinical diagnostic criteria have been thought to have Alzheimer's disease. And hence this kind of conundrum that, well, they've got amyloid, but they don't have Alzheimer's, so how can that be? Our framework has changed now, so that somebody who has amyloid in the brain does have the early brain changes of Alzheimer's, whether they have symptoms and the extent of their symptoms will help with what we call clinical staging. Do they have pre-symptomatic Alzheimer's? Do they have mild cognitive impairment? Do they have dementia due to Alzheimer's? So you can see, it's sort of akin to, you know, if you have a little nest of cancer cells in the breast or in the prostate, we don't say, well, that's not cancer, but it might not be causing any symptoms, and it may or may not warrant treatment. It depends. But that's the stage we're at now. We say, okay, amyloid in the brain, you're on the Alzheimer's pathway. And so are you destined to have dementia right away? No, because there's a lot of years that amyloid has to build up, and then, when it reaches a threshold, tau starts becoming abnormal. So there are multiple things that go on over a long time. I hope that helps, and I know you're not, Jolene, but you had a great question.

JOLENE: Thank you so much. I appreciate it.

NANCY LYNN: Thank you. I'm going to start wrapping up, but I have a few comments. First of all, if you have suggestions for topics, future topics, please feel free to type them into the chat right now. So you can just drop into the chat if there are topics. We are planning for our next episode to address what is frontotemporal dementia? What are the signs?

It was recently announced that actor Bruce Willis has this. Then we'll have in June, I believe it's, yes June, about Alzheimer's and genetics. Is Alzheimer's hereditary? So we hope you'll come back for those. And you will, of course, be contacted about those. I also want to mention, I would be remiss if I didn't that today several times clinical trials came up, and what we know about Leqembi and donanemab from clinical trials. So I feel I would be remiss without mentioning the importance of participating in clinical trials, if one is able. It really is the way and the only way we get to new therapeutics. And perhaps in the future we'll do an episode devoted to clinical trials that are active or particular clinical trials, if everybody is interested in hearing about that, because this is this is really for you guys.

Also, lastly, I want to thank Michael, who asked a few questions, and he wrote in the chat: I don't have AD. And Michael has permitted me to share. He has had a diagnosis for quite a while now. And his doctors are not sure if it's Alzheimer's disease, if it's frontotemporal dementia, if it's some mix. And the reason I'm bringing it up, besides, to thank him for everything he does to advocate for more openness about the disease, and really being the voice of people who have the disease in our field, there's a lot we don't know. And I'm sure, Dr. Cohen, you would agree with me there. There's a lot we still don't know about these diseases, and the fact that he's in this, going through this journey, not knowing exactly what he has. First of all, I think it's very brave, and thank you for sharing and participating in these forums. But also it reminds us that there's still a lot of work to be done to understand different dementias, and how they how they act in us. And then what cocktails of drugs or lifestyle changes, which is another thing we should talk about. Lifestyle mitigations that we can enact.

So I want to first, thank Dr. Cohen, who I have to say is one of the best communicators in our field, and one of the kindest doctors in our field. So we're very grateful to you. You're doing this, our first episode today. If your questions were not answered. We will try to answer them by email, if they were relevant specifically to this topic, to Leqembi. And if they were more general then we'll try to address those in future episodes. If your question was not answered, or you have a new question specific to Leqembi, or if you have suggestions for future topics, you can email this this address reply@brightfocus.org and we will again try to get back to

as well as many people, as we can.

We also can send you for free some publications that we have about Alzheimer's disease. The names of these brochures are here, and so if you would like to request free copies of any of these brochures, the number is below. You can call 855-345-6237 or email info@brightfocus.org.

And I think one more slide and a last slide. Please save the date for Thursday, May 18th. We will be talking about frontotemporal dementia and are looking forward.

I want to mention one last thing. Several people submitted questions in advance on Leqembi subject about whether there was any financial assistance available, whether you have coverage, if you don't have coverage, and all of those things. I just want to mention that on the website of the companies that have created this therapeutic, they are Eisai and Biogen, there is a telephone number where you can ask about financial assistance. That telephone number is 833-453-7362. That is the line that they gave, and you can find it on their website. If you have questions about financial payments, or you know how to actually access the drug, I'll say it one more time, 833-453-7362.

And with that we're going to wrap up. Thank you again. Dr. Cohen. Thank you all for participating in this first episode. I'm going to say be well, take really good care of your health and spend quality time with people that you love, and we'll see you next time. Thank you for participating.