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Early Clues, Lasting Impact: Detecting and Treating Alzheimer's Disease in Its Earliest Stages

Announcer:
Welcome to CME on ReachMD. This activity, titled "Early Clues, Lasting Impact: Detecting and Treating Alzheimer's Disease in Its Earliest Stages" is provided by Clinical Care Options, LLC dba Decera Clinical Education.

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Moderator:
Hello. Good evening, everyone, and welcome to tonight's CME webinar. Our topic tonight is "Early Clues, Lasting Impact: Detecting and Treating Alzheimer's Disease in its Earliest Stages." This is provided by Clinical Care Options, now operating as Decera Clinical Education, and we are supported tonight by an educational grant from Novo Nordisk.

Our expert faculty are Dr. Anton Porsteinsson, who is from the University of Rochester in New York, and Dr. Vijay Ramanan, who is from the Mayo Clinic in Rochester, Minnesota. Sorry, I'm having trouble advancing the slides. You can see their disclosures here very briefly. The learning objectives that we're going to be covering tonight are "Implement evidence-based approaches to incorporate cognitive screening tools into routine practice for earlier identification of Alzheimer's disease; explain the underlying mechanisms of Alzheimer's disease, including amyloid and tau pathology, neuroinflammation, and other emerging pathways; apply current evidence supporting novel diagnostic strategies, including biomarkers, to identify early Alzheimer's disease pathology in clinical practice; and evaluate the latest clinical efficacy and safety data for current and emerging treatment for Alzheimer's disease.

So we're going to start with a few polling questions. The first poll: How many people with Alzheimer's disease do you provide care for in a typical week? Is it 1 to 4, 5 to 10, 11 to 15, 16 to 20, more than 20, or not applicable if you don't provide patient care?

And now for our CME questions, the first pretest. Which one of these cognitive screening assessments is relatively weakest for the detection of early mild cognitive impairment? The Mini-Cog; the Mini Mental Status Exam, MMSE; the Montreal Cognitive Assessment, MoCA; or the St. Louis University Mental Status Exam, SLUMS? Please vote.

All right, second question: Which pathologic feature is most closely correlated with the emergence of clinical symptoms in Alzheimer's disease? A) amyloid plaque burden, B) tau tangle burden, C) markers of neuroinflammation, or D) serum amyloid tau ratio? Please vote again. And these will be covered by the presentation tonight, so if you don't know the answer, please pay attention. We'll ask you again at the end.

Third question: Real-world data demonstrating the accuracy of the Lumipulse plasma assay, the first blood-based biomarker test cleared by the FDA for diagnosis of Alzheimer's disease in May, 2025, were presented recently at CTAD 2025. What is measured by this assay? Is it Aβ42/40 ratio? Is it p-tau 217 alone? Is it p-tau 181 alone? Or p-tau 181/217 ratio? Or p-tau 217 Aβ42 ratio? Okay.

And then our final question: Which statement summarizes the top-line results presented at CTAD 2025 from the randomized placebo-controlled phase 3 trials EVOKE and EVOKE+ for semaglutide treatment in patients with early-stage Alzheimer's disease? Significant slowing of cognitive and functional decline, no significant slowing of cognitive and functional decline, significant slowing of cognitive and

functional decline in patients with MCI but not those with mild dementia, no significant slowing of amyloid plaque accumulation, or significant slowing of amyloid plaque accumulation but no significant slowing of cognitive and functional decline? Please answer.

All right, so I'm now going to hand it over to Vijay to start going through the Alzheimer's disease basics. Vijay, please go ahead.

Dr. Ramanan:
Nice to see everybody. I'll just briefly set the stage. The focus of most of this discussion is going to center around Alzheimer's disease. Biologically, we can conceptualize AD as being defined by two hallmark pathologies, amyloid plaques in between the neurons and tau-containing neurofibrillary tangles within the neurons. It's thought that the underlying nuts and bolts of the disease actually evolve over a long time, over up to 10, 15, or even 20 years prior to the development of cognitive symptoms related to the disease, and the thinking is that accumulation of amyloid plaques, perhaps activation of other mechanisms like neuroinflammation and others, eventually contributing to tau seeding and spreading, degeneration of the brain cells and their underlying synaptic connections, and so this really creates the conditions where we can think about Alzheimer's disease as having a preclinical or asymptomatic phase where those nuts and bolts are building up, followed by a symptomatic phase where there's progressive cognitive decline.

Now, amongst those pathologic elements, research supports that tau burden in the neocortex, and particularly that relationship of tau to synaptic loss and the poor health of the brain cells, that that change, that tau burden is really the most closely correlated with the emergence and progression of cognitive symptoms, that amyloid plaques do accumulate over a long period of time prior to that but are relatively more disconnected from the emergence of cognitive symptoms downstream. With all that in mind, we can then have a concept about AD targeting therapeutically, perhaps ideally looking downstream as targeting multiple of these underlying biological aspects or pathways or mechanisms within the disease. And it may be similar to other health conditions that are complex and chronic that individualized multifocal treatment targeting is where the field is headed, so we'll discuss today some of the emerging developments around amyloid targeting therapies, in particular their use in the early symptomatic stages of Alzheimer's disease, some ongoing trials actually testing whether those amyloid targeting therapies might have roles even earlier in our biological concept of the disease in individuals who are amyloid positive but may not be cognitively impaired as a manner to prevent or perhaps delay the development of cognitive symptoms downstream, but many other mechanisms being either targeted or planned for targeting through clinical trials and translational research, including targeting tau, inflammation, synaptic degeneration, senescence, and other mechanisms.

Now, taking a step back—again, most of this talk will focus on Alzheimer's disease, some of the latest research on that disorder—for a patient with cognitive symptoms, important to keep in mind that AD is not the only potential explanation for those cognitive symptoms. This reinforces being careful, thoughtful and systematic in evaluation of patients who have cognitive symptoms themselves or have a collateral history where there is a concern for cognitive decline. Part of that systematic assessment really can rely on a good quality history, preferably from both a patient and an informant, a collateral source, as well as a standardized cognitive screening assessment. And there are many different screening assessments that can be valuable as a part of this. Examples might include the Mini-Cog. At the Mayo Clinic, we use something called the Short Test of Mental Status. There's the St. Louis University Mental Status Exam, the MoCA; the MMSE. All of these have a role in giving a Gestalt assessment of do we think there might be frank cognitive impairment in this individual.

Now, none of those screening assessments is perfect. They all have their strengths and weaknesses. Amongst the ones that I mentioned, the MMSE generally thought to be less sensitive for picking up, perhaps, early or subtle changes in keeping with mild cognitive impairment, perhaps related to some of the preferences in terms of cognitive domains that that test assesses. Of course, the MMSE has other roles. It's commonly utilized as a, as a follow-up measure in clinical trials and in other settings, so certainly has its uses, but perhaps relatively less sensitive for picking up earlier subtle changes of mild cognitive impairment. Again, relative strengths and weaknesses of some of the other tools that I mentioned.

There are also expanded versions of cognitive assessments, neuropsychological testing in particular, and this may have slightly different roles in today, 2026, compared to in the past. For example, in delineating, does a patient with cognitive symptoms have impairment, meeting criteria for MCI or dementia, or is that patient subjectively having cognitive symptoms but really performing normally from a cognitive standpoint? It's a great use for neuropsychological assessment. For some of the new treatment options for Alzheimer's disease, we don't have evidence that those treatment options have a benefit in the later symptomatic stages of disease, so characterizing the severity of impairment sometimes can be very helpful, particularly for border zone cases and in cases where perhaps the scenario is atypical. Other testing has not yielded an etiologic diagnosis. Characterizing the pattern of impairment across cognitive domains can be helpful in narrowing that etiologic diagnosis and differential. And great news for patients and for clinicians involved in care, that we have now excellent and continued development in biomarkers, which can give readouts about that underlying biology perhaps related to Alzheimer's disease, as we'll talk about later today, but also biomarkers in practice and in development for other neurodegenerative conditions which can cause cognitive impairment.

And the point of all of this is being systematic. Utilizing those screening tools and biomarkers in a thoughtful way helps us to get confident diagnoses for patients, and diagnosis is the first step to therefore defining appropriate expectations and selecting the right combination of management options for that individual. We know that thinking about issues around dementia, Alzheimer's disease and related conditions can be weighty. There can be stigmas about those things. But just as with any other health condition, intervening early seems to be a major emphasis, and identification early is part of facilitating that early intervention.

With that, we've got a lot to talk about in terms of updates and research in the field, starting with some things presented at a recent meeting at CTAD, and I'll hand things over to my colleague, Anton, to take over for the next phase.

Dr. Porsteinsson:
Thanks. Thanks, Vijay. This was a great introduction. Sorry, everyone. So you heard about basically the pathology that emerges in terms of the plaques, the tangles, the neuroinflammation and the oxidative stress, metabolic derangement that predates then the onset of clinical symptoms. So we know that you don't wake up one day having Alzheimer's disease. And what makes people more vulnerable than others? So part of it is your genetic makeup. There's an autosomal-dominant variant of Alzheimer's disease, rare, but for those families, there is basically 100% penetrance. There are also other genes that may increase your risk, like APOE4. If you're a carrier of one or particularly two copies of APOE4, that really increases your life, your lifetime risk. But we also know that lifestyle, diet, and exercise, for example, have a major impact, and this is being better established in clinical trials. So, many of you may have heard about the FINGER study, which was conducted in Europe. And then the Alzheimer's Association basically supported the U.S. POINTER study. So here you have a phase 3, single-blind, two-year, multi-domain lifestyle intervention trial. So they enrolled people that were between 60 to 79 years old that were at risk for developing dementia. This is over 2,000 participants. They were cognitively normal, and then they were randomized 1:1 to either structured intervention versus self-guided intervention. And what the focus was on was increasing physical exercise, modulating your diet, cognitive exercise, and health coaching. So, what would this intervention bring about? And what we saw, that over two years, we saw both groups actually improve, and the group that had a structured intervention did a little bit better than the ones that did the self-guided intervention. And this benefit, even if it looks small on the graph, it was statistically significant and pretty robustly so. So this matters. When people come to us and say, "What can I do?" and they're still cognitively intact but they may have a family history or otherwise, you can tell them that healthy lifestyle, healthy diet, adequate exercise, addressing some of the medical problems, being compliant with treatment, actually makes a difference. It bends the curve, the risk curve here.

So this basically can be reflected in some of the measures that you saw previously. So not only in cognition, but there were some impact on brain structures, so for example, on, on hippocampal volume. And again, we could impact on sleep, for example, reduce apneic episodes like an obstructive sleep apnea, and we could see an improvement in reflux sensitivity and also in basically cardiac variants where you see the amount of fluctuation in heart rate, so there are multiple things that healthy lifestyle brings to the table.

We're going to come back to probably one of the hottest topics in our field currently, and that is the emergence of the rapid development of blood biomarkers. And there was a very intriguing study, real-world study done at Mayo, so, Vijay, you're a home base. What did this study show us?

Dr. Ramanan:
Thank you, Anton, and I will echo what you said. It's like every other week we're seeing a new, high-impact paper about blood-based biomarkers, and I think this is a, a great thing for the field to have additional tools to help with diagnosis, potentially with even treatment monitoring with additional research in the future. But to kind of contextualize this conversation, as I mentioned earlier, if we're suspicious that a patient may have Alzheimer's disease as the reason for their cognitive difficulties, appending biomarkers is actually critical. In part, if you're thinking about therapies that target specific aspects of the biology of Alzheimer's disease, like amyloid plaques, you really need to know are the amyloid plaques there in the brain to begin with, because not every patient with a memory-predominant cognitive decline syndrome at late age is going to have Alzheimer's disease. They may have an alternative diagnosis, like late or Lewy body disease or other conditions, so biomarkers are critical for trial design, critical for new treatment options, critical for accurate diagnosis more broadly.

We have had over many years a variety of biomarkers in the toolkit. Amongst imaging biomarkers for looking at amyloid plaque presence, amyloid PET has generally been considered the, the gold standard. It's not perfect. No biomarker is. There are very rare cases of genetic, typically genetic Alzheimer's disease where there may be issues with the binding of an amyloid PET tracer to the peptide and the amyloid beta plaques even though that individual has amyloid plaques in the brain but a very high-quality test generally in the field considered a gold standard in life for detection of amyloid beta plaques. We also have CSF biomarkers which can give a readout of that Alzheimer's disease pathophysiology, and I think a lot of experience in the field with use and interpretation of those biomarkers, generally quite high concordance between good-quality CSF biomarkers and amyloid PET.

Having said that, both of those modalities have weaknesses. So, for amyloid PET, it requires a lot of things, requires a PET scanner,

requires access to tracer, typically would require access to an expert neuroradiologist or someone else able to interpret the images. These are not things that necessarily may be widely available throughout clinical practice settings. With CSF biomarkers, there's the requirement for a lumbar puncture, which I consider a safe procedure, but it is an invasive procedure. There is the requirement of some expertise technically to perform the procedure, and in particular for those CSF biomarkers, there are collection issues which can be important for interpretation. If the wrong type of tube is used, for example, to collect the fluid to run that test, we know that amyloid beta proteins in particular can be quite sticky and stick to the tube and, therefore, alter the ultimate readout of those biomarker tests. So point being, it would be a great thing. It has been the discussion in the field of how positive it would be to have good quality blood-based biomarkers supporting an Alzheimer's disease diagnosis, potentially for cost-effectiveness, potentially for wider access as well throughout a variety of clinical practice settings.

In recent years, fortunately, there's been rapid development in blood biomarkers, and there are many different blood biomarkers potentially relevant for Alzheimer's disease, many different assays, different labs that are running those biomarkers. And important to keep in mind, those different assays, those different labs, there can be differences, sometimes meaningful differences in accuracy, in false-positive and false-negative rates. And as we know with any test, it's important not just to have the initial development of the test and even the validation in early cohorts but also the real-world experience to back up how those tests can be thoughtfully utilized. So the study that Anton mentioned—and to mention upfront, I'm one of the co-authors on that study, but that study is led by Alicia Algeciras at the Mayo Clinic—was looking at a recently FDA-approved test from Lumipulse. Specifically, the assay is looking at the ratio of phosphorylated tau at position 217 to Aβ42. Again, recently, FDA cleared a lot of news articles and press about this and interest potentially in utilizing this test more broadly in clinical practice. The goal here was to see how well did that test perform in a cohort of individuals seen at the Mayo Clinic and mostly for evaluation of diagnosis and/or for new treatment options.

One of the interesting components here is that there was a, again, gold standard of truth in many of these patients having either amyloid PET or CSF biomarkers to give us a comparison measure of their amyloid status. And in looking at that FDA-approved Lumipulse assay p-tau 217 to Aβ42, one of the surprising findings was that a nontrivial proportion of individuals who were amyloid negative by either PET or CSF, which have been well validated in practice for a long time, would have been classified as positive or abnormal by that p-tau 217 to Aβ42 ratio. In particular, about 40% of the amyloid-negative individuals would have been classified as amyloid-positive by that blood-based biomarker, so a lot of discussion at the meeting and afterwards about why that finding may have been the case. And some ideas coming up about "Well, could that be related to specifics of the cohort? Could that be related to the cutoffs utilized for positive or negative?" Or as with some assays, there might be a two-point cutoff approach where individuals are classified as negative hoping that below that value you're at a high likelihood of a negative amyloid PET positive, where if above that value, you're at a high likelihood of a positive amyloid PET, and then an intermediate range where there may be a need for a complementary biomarker. But the idea that 40% of these individuals who were determined amyloid-negative by another high-quality biomarker would have been found positive on this blood test has really led to some pause and a broader thought that we really need continued research in real-world cohorts to understand how these assays perform, because there could be a variety of contributors to those findings. As I mentioned, cohort issues, cutoff issues, some discussion about whether reagents and batches may be factors, whether preanalytical things, similar to what I had mentioned earlier about CSF biomarkers in terms of the collection and stickiness of that amyloid beta protein to tubes and the kind of finicky nature of measurement of that protein and how it may impact the ratio. But point being I think a high-quality research study continuing to advance the field by leading us to ask questions and hopefully narrow in and hone in on the highest-quality readouts in terms of blood-based biomarkers and how they perform in real-world clinical settings.

Dr. Ramanan:
It's critical for us to, to dig into there, and, and perhaps maybe we can start, Anton, with your thoughts on kind of the, the general status of blood-based biomarkers in the field where you see some of the, the challenges and also the opportunities.

Dr. Porsteinsson:
So it's interesting, Vijay, because we had been doing p-tau 217 blood biomarkers alone in our clinic, and we were pretty happy with it. When the FDA cleared the Lumipulse p-tau 217 Aβ42 ratio, we slowly decided to switch. Why did we do that? Because we thought that an FDA approval would simplify insurance coverage, and also, we were getting some pushback when we tried to get insurance coverage for the humanized monoclonal antibodies against beta amyloid lecanemab, and donanemab with a blood biomarker. We would get pushback, and they would say, "Hey, this isn't FDA approved." So we ran into at least four cases where the test was positive, but after we saw the results from your study, we decided that we wanted to check this further. So they were between getting a blood biomarker and starting treatment, and we were able to squeeze in a PET scan, and this was for a reasonable group of people. We, we had four cases where they were positive on the blood biomarker but negative on an amyloid PET scan. They all had clinical symptoms, but their dementia was due to something else. So we've actually gone back to the p-tau 217 alone, because the suspicion is, to some degree, either that the reagent coming from Lumipulse was flawed for, you know, these batches, or that there is this sensitivity and that

Aβ42 can be absorbed if the sample is not prepared accordingly. So blood biomarkers are, are increasing significantly in, in my clinic. In fact, most of the new patients, if they have clinical symptoms, are getting blood biomarkers first, and even quite a few that come in with atypical presentations because there's information here. At least you can say, "Well, it doesn't seem to be due to an elevated amyloid plaque burden that you're having this." And for both treatment and for patients, that has been surprisingly well received. We haven't done the p-tau 181, which was approved for kind of primary care. Not yet. And we're waiting because there—the interesting thing about a p-tau 217 test is that it predicts amyloid burden. It is not as good at predicting your tau tangle burden even if it is a tau isotype. So we expect to see more blood biomarkers be FDA approved in the near term. For example, C2N with Precivity, and others. We may see Roche come into this market as well with a p-tau 217. But we're also waiting to see the kind of mid-domain or the microtubule binding region tau/p-tau fractions that may predict tau tangle burden better. But what are you doing? What are you seeing? What's kind of the, you know, standard in, in, in your clinic? And are you—

Dr. Ramanan:
I couldn't agree. I couldn't agree more.

Dr. Porsteinsson:
Are you seeing—

Dr. Ramanan:
I think you outlined things very, very well. We've been similarly very pleased with the p-tau 217 assay. It's one of the most commonly used tests now I think in our, in our memory clinic, also in general neurology settings as part of early screening in patients who have cognitive symptoms as a, as a rule in or a rule out in some of those unusual situations, as you mentioned, for Alzheimer's disease. And I think A) you're absolutely right. It's a common point of confusion. You've got a, a protein of tau, but really what it's reading out to you is that Alzheimer's pathophysiology is there in the brain. The concordance is with amyloid status and amyloid—positive amyloid PET scan. And it will be really fantastic as we look to the future, similar to how we approach lipid management, other disorders where there may be multiple blood-based biomarkers that are each giving you some unique information, and you can use that to then target for potentially trial screening, therapeutic selection, potentially other tests in some cases. So I think that the field is moving positively, and that's a really good thing.

One of the discussions that this issue buttresses up against is when and whether the field would be comfortable with initiating goal-directed treatments, amyloid-targeting treatments, based on a blood biomarker test alone. I think there's some variation in practice around this. At our center, we are, again, using the blood tests in early screening to help with diagnosis confirmation, but for patients that we're really seriously considering for anti-amyloid therapy, we're still preferencing trying to get an amyloid PET scan or, at minimum, CSF biomarkers prior to that. Is that something that could evolve in the future, perhaps with very, very straightforward cases? I think continued research is going to be, be the key to, to that discussion.

Dr. Porsteinsson:
And are you seeing many primary care practices in your area using blood biomarkers, or is that still mostly in the specialty clinic?

Dr. Ramanan:
That's a great question. Our experience is certainly growth in primary care practices. One of the benefits I think we've tried to be, in a dedicated way, tried to share education about these blood biomarkers, about how to interpret the blood biomarkers, about some pitfalls in interpretation—for example, patients with significant chronic kidney disease that can artificially inflate the level of p-tau 217 in the blood—and so these are things that have to be taken into account with ordering and with interpretation. My sense is still, because of some of those nuances and the rapid evolution of knowledge, these are still most commonly being ordered in neurology settings and especially specialty settings, but we've seen tremendous growth in general neurology and even in some primary care settings with the ordering of this test.

Dr. Porsteinsson:
And, and we, we are seeing—having basically the same experience as well. So let's move on, and I'm going to talk about the results for EVOKE and EVOKE+. And these where studies of semaglutide, a GLP-1 agonist, in early symptomatic Alzheimer's disease, so the same population as is being treated with the humanized monoclonal antibodies, so mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease as well. So, why would someone use a GLP-1 agonist for Alzheimer's disease? Well, there is some preclinical evidence that this would make sense, but in addition to that, we have very strong epidemiological data from both previous studies of people with diabetes and obesity as well as data from large healthcare systems or countries where there is a single health system and that show that there's a lower emergence of all-cause dementia in people that are on GLP-1 agonists. And Novo Nordisk ambitiously decided to explore this, that there was enough promise there, that they designed two very large studies based on kind of what they knew preclinically, and that is What does semaglutide do? Well, it improves your glucose control, and some people

have referred to Alzheimer's disease as diabetes type 3, kind of like a brain diabetes. We also know that neuroinflammation is, is common and that the GLP-1 agonist can decrease systemic inflammation at least, and the hope was that that would translate into the brain as well, that metabolic stress is also reduced with the GLP-1 agonist, and that as a whole this would be the foundation for why we are seeing in, in, in kind of real life the reduction in the emergence of all-cause dementia. Let's though remember that the populations that they were looking at were preclinical. These were not people that had already developed memory impairment but were cognitively intact at the time, that appeared cognitively intact when they started with semaglutide.

So two studies, they used the oral version of semaglutide, so Rybelsus, and they titrated people up to 14 mg of semaglutide, oral semaglutide daily. And these studies had over 1,800 participants each. They were identical, except for EVOKE+. The aim was that about 20% of the participants would have more kind of cerebrovascular burden. They didn't quite get that. You know, when you're looking for something, we think that we see mixed dementia all the time or that we see so much kind of cerebrovascular burden, but when you're looking to recruit these people into trials, it is not as easy, and that was the results here. They got about 11% of participants that had high cerebrovascular burden. Well-designed study—I'm not going to go into all of the details—well-executed, using outcome measures like the clinical Dementia Rating Scale, some of boxes that we saw as the primary outcome measures in the humanized monoclonal antibodies. And basically, these were patients with MCI due to AD, mild AD. They were biomarker verified, 55 to 85 years old. And they recruited a group that was more likely to decline.

And what was very disappointing in this study—and here we were looking at basically the main outcomes were at two years, so 104 weeks, but the study continued for a full three years, so that's why you're seeing 156 weeks here on the graphs—but there was no difference between drug and placebo in terms of decline over the course of two and then even three years, so very disappointing, actually. For me, this was something that I had been quite hopeful for because up to this point, the GLP-1 agonist seemed to be kind of having a protective effect on so many end organs, the kidneys, the liver, the heart, besides diabetes, but the brain in this population, we didn't see much of a difference. This was basically seen on global measures. This was seen on activities of daily living and time to progression. There, you know, regardless of the main measure, we didn't see a difference. And the overlap was so tight that, you know, the leaders of the study were asked, "Do you expect that there will be some subgroup here?" for example, APOE4 homozygote carriers that will have preferential benefit, and the answer was it's, it's actually unlikely because the, the overlap was so very, very tight. We will see that detail when we go to the ADPD conference, which will be in Copenhagen in mid-March. And Nicola mentioned before that she's planning another webinar about the main findings there right after the study.

So people have asked me, "Were there—" you know, "Was there compliance? Did people take the drug? Was there any evidence that they took enough?" And yes, blood glucose looked better. Markers of systemic inflammation looked better. The compliance was surprisingly good. So this was not because we underdosed or that people dropped out because of side effects or something of that nature. Study was well done, well executed. And, you know, when you looked at biomarkers, both CSF and blood biomarkers, there was also not a very clear picture. And in fact, when we found something in the CSF, it went the other way in the blood biomarkers, so as a whole, there didn't seem to be a convincing picture except for the fact that the drug did in the periphery what we would expect it to do.

In addition to that, basically, you know, we, we, we know that in, in other studies with the GLP-1 agonist, we continue though to see titillating evidence that somehow there, there's a difference in what is called proteomic dementia risk that used the subcutaneous semaglutide as opposed to the oral version, so we're, we're, we're trying to still figure this out. But I, I think that the consensus was disappointing results. Still some intriguing impact on the markers that we think increase your risk overall, but maybe we need to move earlier to a preclinical population. So very disappointing to me to see the results.

Vijay, what do you—what was your sense here? What was your reaction?

Dr. Ramanan:
Similar. I think both of us and everybody joining would like all the tools we can get to treat Alzheimer's disease. I think there was hope that there may be a positive signal out of this report, and unfortunately, none coming, so I don't think we have an indication for these drugs in, in clinical practice as a treatment for Alzheimer's disease at this time. It reduces maybe the enthusiasm of that idea, but as you mentioned, Anton, I don't think that necessarily ends the story of investigation of these agents. Some thought about, you know, really is the time to utilize these, say, after amyloid has been cleared, or is really we need to move the needle earlier to before there are some other biological aspects of Alzheimer's disease, or is the right substrate in vascular cognitive impairment? So I'm sure more studies to come, and some of that omics data and biomarker data may feed into those studies.

Dr. Porsteinsson:
And so with that, I think that the focus right now remains very much on the humanized monoclonal antibodies and that, that target beta amyloid plaques, in particular is lecanemab and donanemab. And there was some data on that. You know, we're seeing subcutaneous lecanemab come to the market for at least maintenance treatment and maybe later this year for treatment initiation. So, can you tell us

what we saw in terms of that at the CTAD?

Dr. Ramanan:
Absolutely. And so, as Anton had mentioned, subcutaneous formulation of lecanemab is now available for use in maintenance therapy, and this is fairly specific to lecanemab itself. So after 18 months of receiving the induction with IV lecanemab, patients could transition to either monthly IV lecanemab for maintenance or now a weekly subcutaneous injectable form of lecanemab for maintenance. And we'll talk briefly about just the concept of maintenance therapy, because again, it's different from the mode of operation with donanemab, where really it's a treat-to-clear philosophy. But the availability of that subcutaneous form, at least for maintenance currently, is also a factor in broader consideration of whether that subcutaneous form of lecanemab could be utilized as an alternative to the IV formulation for initiation of treatment, and so some data presented at CTAD really indicating essentially equivalence in terms of exposure of the drug to the central nervous system where it's intending to act, in terms of the safety profile in relation to the IV formulation, you know, can have a grain of salt with this, but perhaps even a little bit less of ARIA or infusion reaction type symptoms after administration of this as compared with the IV formulation.

And so thinking ahead, there is an application for this formulation to be potentially reviewed and approved by the FDA for initiation of treatment. We're thinking potentially we may hear some updates about that later in 2026. And thinking ahead, there could be some advantages for some patients and care partners in having that formulation. For example, for individuals who may qualify for anti-amyloid therapy but may be fairly remote from an IV infusion center, the ability to dose the medication at home and limit travel from that standpoint could be an advantage, may also give some patients greater flexibility in terms of making this therapy a little bit more similar to some of the commonly used medication therapies out in the community.

But as we think about some of that backdrop, Anton, how would you envision, you know, patient selection or utilization of this subQ form if it is approved for maintenance?

Dr. Porsteinsson:
So a lot of our patients, and we are right at the point now—We were slow out of the gate to get all of our operations up and running, but we have now a number of people that are completing 18 months of lecanemab. And interestingly, Vijay, in our clinical trials, because I did the clinical trials with both the IV and the subcutaneous version, there a lot of people were hesitant to go on the subcutaneous treatment, and it was because they had formed such close relationships at the infusion center, at the research infusion center, so I wasn't quite sure what to expect. But the commercial infusion centers, I don't think that there's quite the same connection. So a lot of these people are—they've been doing IV infusions for 18 months, and there, there seems to be much more excitement about going to basically auto-injector subcutaneous delivery even if now with maintenance treatment you can go to monthly infusions, so a lot of people want the freedom. They say, you know, "I've done this. I want to be able to travel." These are people that have mild disease, still pretty functional.

For initiation, I think we have to be a little bit thoughtful. The ARIA risk is most significant in the first three to six months. And when you have people come into the infusion center, there's kind of a nurse that talks to them, maybe asks them if they have had any clinical symptoms, et cetera, et cetera. You lose that when it's at home. So you will need to set something up to, to kind of maintain that communication, that people will go and have their MRI done at the right time and don't skip the MRI and continue giving themselves injections. So we're figuring that out, but there definitely is a patient population that you highlighted, those that have longer distances, those that are more autonomous, want to travel, et cetera, et cetera, so it will be interesting to watch.

I'm going to talk a little bit about the—Maybe the most controversial presentation or that created the most ruckus was a presentation that was done by a friend of mine, Suzanne Hendrix at Pentara. She's actually a statistician but pretty clinically astute. So she looked at publicly available data from the CLARITY studies of lecanemab, of the TRAILBLAZER ALZ-2 studies of donanemab, and looked at the extensions, and then she kind of statistically modeled the, the course. There's been a lot of, you know, debate. Can you treat until the amyloid plaques are completely gone and then to stop treatment like you do with donanemab, or is there any advantage to continuing treatment, like with lecanemab, that may have a broader binding profile, both to plaques and soluble species? And according to her assessment, there was a greater ongoing slowing with lecanemab than donanemab, but this caused a, a, a pretty fierce pushback from the Eli Lilly camp in basically saying, you know, "You're, you're, you're not comparing just apples to oranges; you're comparing apples to steak; so you can't do this." Her response was, "Give me your, your data, both sponsors, and then I can do this modeling better."

But in the interest of time, I'm going to quickly talk about also kind of what we're seeing, and that's brain shuttle technologies. Here we actually have antibodies that bind to basically the transferrin receptor in the brain, which helps increase the amount—it kind of increases by tenfold the percentage of the antibody that gets across the blood-brain barrier, and this is really the next generation of kind of antibody treatments targeting anything in the brain. And trontinemab is basically the main, the first in this group. And basically, we have data from a phase 2 study that suggests that there's remarkable amount of amyloid clearance in just seven months. Over 90% become

fully amyloid-negative and with much lower rates of ARIA-E and ARIA-H. So these are the complications, the, the, the localized brain swellings that you can see as complications, whereas, you know, you see about 12.5% with lecanemab and about 24% with donanemab. Here it was under 5%, even in the APOE4 homozygotes, which are at most risk.

So I'm not going to go into the details. I'm just going to say that there's a—there are two phase 3 studies going on right now of trontinemab, and we will basically see if the phase 2 data holds up, that we may get a humanized monoclonal antibody that has some pharmacokinetic and pharmacodynamic advantages and is associated with more rapid amyloid clearance and, and lower side effects, at least the, the ARIA rates.

And with that, how about you giving us a quick overview of tau-targeting therapies?

Dr. Ramanan:
Yeah. And again, in the interest of time, just to maintain that optimism that Anton mentioned, as we emphasize these anti-amyloid therapies, and particularly, how can we better deliver them more safely, more potently, there's equal attention on other mechanisms relevant for Alzheimer's disease, so, many compounds looking at targeting tau. It's a tougher element of the biology to target, being an intracellular, but a variety of techniques being utilized in early-phase trials to target tau and ideally, really, the field heading towards a combination type approach and testing in some patients tau-only therapy, in some patients amyloid therapy plus tau therapy, and that really offering a window into the future of how we may approach Alzheimer's disease, how we may end up extending some of these concepts into related neurodegenerative conditions, so I think a lot of reason for optimism. And in this aspect of things, tau- targeting, some data yet to bloom here over the coming years, as you see on this slide.

So with that, I might hand things back to Nicola. We'll have some questions for the audience to go for again.

Moderator:
Okay, thank you. Thank you both. And apologies that we didn't quite have enough time to fully cover everything. There really, there really is a lot here. So, if we could go through the post-tests. Let's see. All right, so the first post-test question: If you remember, which of these cognitive screening assessments is relatively weakest for the detection of early mild cognitive impairment? Is it the Mini-Cog, the Mini Mental Status Exam, the Montreal Cognitive Assessment, or the St. Louis University Mental Status Exam? Please answer. All right, I see 78% of you answered that one correctly, so good job.

Next question: Which pathologic feature is most closely correlated with the emergence of clinical symptoms in Alzheimer's disease? Amyloid plaque burden, tau tangle burden, markers of neuroinflammation, or serum amyloid tau ratio? Please answer. And I'll wait for the answer statistics to come. All right, divided there. The answer is actually tau tangle burden. The neuropathologic change that correlates best with the severity of clinical symptoms and cognitive loss is the extent and distribution of synaptic loss, neurofibrillary tangles in particular.

Question number three: Real-world data demonstrating the accuracy of the Lumipulse plasma assay. What is measured by this assay? Aβ42/40 ratio, p-tau 217, p-tau 181, p-tau 181/217 ratio, or p-tau 217 Aβ42 ratio? Please answer this one. All right, 65% of you have gotten this one correct. The answer is the last choice, p-tau 217 Aβ42 ratio.

Final question. Oops, there it is. Final question: Which statement summarizes the top-line results from the randomized, placebo-controlled, phase 3 trials EVOKE and EVOKE+ with semaglutide in early-stage Alzheimer's disease? Significant slowing of cognitive and functional decline, no significant slowing of cognitive and functional decline, significant slowing of cognitive and functional decline in patients with MCI but not those with mild dementia, no significant slowing of amyloid plaque accumulation, or significant slowing of amyloid plaque accumulation but no significant slowing of cognitive and functional decline? All right, and again, a lot of you got this one correct. The answer is B) no significant slowing of cognitive and functional decline was seen with semaglutide in this trial.

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