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

The START Study: Testing an Oral Capsule That May Protect Brain Synapses
Thursday, October 3, 2024 | 1 p.m. EDT
Transcript of Zoom with Christopher H. van Dyck, MD
Director, Alzheimer's Disease Research Unit Co-Director, Alzheimer's Disease Research Center Yale School of Medicine

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

NANCY LYNN: Welcome to everybody. We're delighted that you're here. We have a really fantastic speaker today talking about something that I find really fascinating. And I will confess, I wasn't really that aware of it until I started looking for trials to feature here. And I've been doing this for 15 years, day and night. So it's nice to be able to learn more about this for myself and to share it with all of you, since this is a study that is currently recruiting, and I hope that some of you may be able to participate.

So if you have questions on other topics besides the START study, I just want to call your attention to the series that we're doing. On general topics in Alzheimer's, these are all for free, and they're all available for you to watch on our website at brightfocus.org/ZoomIn. And they're on YouTube. So if you're interested in learning more about Kisunla, the new drug that was approved, or early onset dementia or genetics in dementia, this is a wealth of information. Please go ahead and access it.

So our guest today, Dr. Christopher van Dyck is professor of psychiatry,

neurology, and neuroscience, director of the Alzheimer's Disease Research Unit and co-director of the Alzheimer's Disease Research Center at the Yale School of Medicine. He is an international leader in the Neuroimaging and Therapeutics of Alzheimer's Disease and Brain Aging, and he has authored 175 peer-reviewed publications. Dr. Van Dyck serves as co-chair for the project evaluation committee and is a member of the executive committee for the Alzheimer's Clinical Trial Consortium, ACTC, funded by the National Institute on Aging. This is a fantastic group that we work with. He received the Distinguished Scientist Award of the American Association for Geriatric Psychiatry and lots and lots of other awards. But I'm going to stop there and just say, welcome, Dr. Van Dyck. We're delighted to have you today.

DR. CHRISTOPHER VAN DYCK: Yeah thank you so much, Nancy. And it really is a pleasure to be here. I want to thank the BrightFocus Foundation for inviting me. I want to thank all of you for attending.

NANCY LYNN: Our pleasure and our privilege. So the START study, we're here today to talk about a study that you are leading with sites all over the country and currently recruiting and START is so easy. But that stands for Synaptic Therapy Alzheimer's Research Trial. So could you kick us off by giving us a big picture idea about the trial and in particular, of course, the oral drug, the oral capsule that you're testing. What is it? What's different about it? And then after that, after Dr. Van Dyck gives us the general introduction to what the study is and what the drug is, we'll start talking about things like eligibility criteria and a lot of the questions you guys sent in. So over to you, Dr. Van Dyck.

DR. CHRISTOPHER VAN DYCK: Now, before you get dizzy looking at this, really, it's not-- I think I can explain this. And it's just really going to be the picture on the far right. But first of all, I think probably many of you are familiar or have heard of the drugs that are now approved, that are the first disease-modifying treatments for Alzheimer's disease. Nancy, referred to one of them, Kisunla. The other one that's out there already in the clinics is Leqembi. So Leqembi and Kisunla. And these treatments do work against the protein amyloid, which many people think is a major factor. Some people think it's the factor in the cause of Alzheimer's disease. So this amyloid protein is bad. I think everyone agrees on that. You can think

of it as a poison or a toxin that then damages our brain cells. So the drugs that are approved, the Leqembi; Kisunla, they work by attempting to remove the amyloid from our brains. They have to be given intravenous infusions. People come in. These are antibody treatments. They're similar to your own natural antibodies. Your own immunity circulate in the blood. They go into the brain. They bind to the abnormal amyloid and remove it from our brains. That's how they work. So this drug, and you see, we call it CT1812, it doesn't have a brand name yet. Well, it actually does, but it's referred to really by its number CT1812. And it is also an anti-amyloid drug. It isn't given as an intravenous. It's given as a daily pill. But what it does not do is attempt to remove the amyloid from our brains. Instead, what it does is it tries to protect our brain cells from amyloid, from its most toxic poisonous forms.

So with that in mind, if you look at the picture on the far right, the poison here is the red, fluffy thing in the right-hand side. Yeah, thank you for that, if you can all see that. But that's the poison. That's the culprit here. And the most toxic form of amyloid is thought to be these oligomers, not the plaques themselves for the most part, but these oligomers, which are clumps of the amyloid protein bound together. But they're still liquid fluid. They move about in the brain, in the fluid around the brain cells. And what happens is, they will bind to the surface. So what's shown here down on the bottom is a membrane, a cellular-- that's perfect. Yeah, that's the cellular membrane. So that's the lining of the brain cell. That's the outside of it. And what amyloid is thought to do in this form is it binds to that membrane. And then it causes things inside of the brain cell that are bad. And it includes, so it results in damage that results in abnormal tau-- another protein tau, that's thought to be important in Alzheimer's. So it can activate that. So it activates a damaging cascade. And so what would be nice is if we could prevent that amyloid oligomer from binding to the brain cell, the outside of the brain cell to the membrane.

And that's exactly what our drug CT1812 does. So it's these little blue semi-circular things, that CT1812. And what it does is it binds to its own receptor, its own target on the cellular membrane. It's called a sigma-2 receptor, which I know is literally Greek. So that's Greek. But it binds to that receptor. And what it does is it causes a deformation of the place

where amyloid would like to bind. So it essentially boots the amyloid off of the cell. So it's not clearing amyloid, but it's kicking it off. And we know that it does that because there's been studies done to show that the amyloid then appears, like in the spinal fluid. It gets kicked off. So that's really, in a nutshell, what the drug is doing-- not lowering amyloid, but protecting the brain cells by kicking it off. And you can see that in theory, that would lead to restoration of a synapse. That's the communication between our brain cell, where one brain cell talks to another for functioning. So it can lead to restoration of those and perhaps actually restoring some cognitive function. And maybe, a more realistic thing is to slow the rate at which cognitive function worsens.

NANCY LYNN: Actually, I want to jump in, if you don't mind, Dr. Van Dyck. Just because before we go to eligibility criteria and stuff like that, I think people are very interested in-- so we have an oral pill, and it keeps amyloid from entering the cells. It's one of the only things I've ever heard anyone say might be restorative, might actually. But even slowing the progression, of course, is really critical to people who have mild cognitive impairment and their families who would like more time with them. But it begs the question, and several people have asked, could they use this--it is not FDA-approved yet. This is still in trial. But if you were in the trial or if it is approved, could you use this if you're also taking Aricept or Namenda or Leqembi or Kisunla or any one of these other Alzheimer's-focused therapeutics right now?

DR. CHRISTOPHER VAN DYCK: Yeah. Well, good questions. And actually, you just asked at least two different questions, which are good, but let me just take them one at a time. So back to the whole idea of restoration. I mean, let me be really, really clear. This is an experimental drug. The trial that's going on right now, the START study, is really the first attempt to actually look at whether the drug is beneficial. There's been quite a lot of testing up to now, but it's been mostly the smaller studies, to work out the dosing, the safety, and so on. So this is experimental, and we should not make any claims about benefit for it.

NANCY LYNN: I'll interject, though, that you said safety, but you have shown that it is safe.

DR. CHRISTOPHER VAN DYCK: We have shown that it's reasonably safe. And every drug, I think, as people know, does have potential side effects. And I'm sure we'll talk about those, too. But the whole idea of restoration, I should actually really point out, that comes from the testing in mice. And mice aren't always the best model for human Alzheimer's. A lot of things happen in mice that we only wish would happen in people. So in mice, it really does. The mice that have been genetically altered to develop amyloid in their brains and tau in their brains. So the model mice, in them, the drug does restore synapses, and it does actually improve them, above where they started. But I really want to be cautious about that because we've seen that before in mice, where it doesn't mean that that's realistic for humans. I would say this, this is an experimental drug. I think the realistic hope for it would be in slowing deterioration, not in bringing people back to where they could do things they couldn't do before. You can think about that a brain cell can be sick, but not gone. And if you can remove amyloid, maybe you can improve some sick cells. So there's a theoretical way that it could make somebody a little better in the near term. But I do think the realistic hope for drugs like this is to slow decline.

And that being said and my memory, let's see your second question was. Oh, can they take other treatments? Yeah. So yes. The drugs that have been approved for a long time, that's like the donepezil or also known as Aricept, rivastigmine, also known as the Exelon, usually, the skin patch, memantine, also known as Namenda. Those are all perfectly fine. We do trials with those as co-therapy or as backbone all the time. The issue with the new drugs, the amyloid-clearing drugs, like Leqembi and Kisunla, is more complicated. And a lot of trials for those of you who have looked at trials, for yourselves or your loved ones, you know that they do have a lot of exclusions. And in general, trials would not permit a drug like that because those are having their own effects on amyloid. They're clearing it. So how are you going to look at the effect of bumping amyloid off of neurons or brain cells if you're already on a drug that's clearing it? And so that's a roundabout way of saying this. A person, if they enter the START study, they can't start a drug like Kisunla or Leqembi in the middle of the trial. That would just introduce too many confounds. We wouldn't be able to know what's going on. And if they had side effects from those drugs, we wouldn't know what was causing what. But the good news is,

if a person is already on Leqembi or Kisunla, they've already started them, once they've been on them for a full six months, at least six months-- so they're really stable, they're past the period when side effects usually occur on those drugs-- then they can enter this trial on those drugs. I want to emphasize, that's actually very unusual for anybody who's looking at trials. Very unusual. And we're really proud of that, that we're pioneering that kind of thing of allowing these drugs as background treatment. So they are allowed once stabilized for six months.

NANCY LYNN: Just to get this part out of the way, so to speak. Roger, can you bring up the slide with the eligibility criteria? Just for those of you who really are here to see, is this a trial I can participate in? I'm just going to read it off. To be potentially eligible for this trial, here are the basics. And thanks, Alexa just put the web page and the phone number to call if you're interested into the chat. But again, we will send it around. But here it is-- https://start-study.org or 1-833-782-7833. So you would potentially be eligible if you're between ages 50 to 85, have a diagnosis of mild cognitive impairment, MCI, or mild Alzheimer's disease, dementia. You'd be required to be able to make around 24 office visits about 20-month commitment. You would be willing to take an investigational oral treatment, and you would have a study partner throughout the study.

And I want to say two things here. One is to Dr. Van Dyck saying this is an experimental drug. I just want to emphasize that pretty much, any drug in a drug trial that has not yet been approved is an experimental drug. And so while I think Dr. Van Dyck is showing the appropriate caution and speaking very responsibly, it doesn't mean it's iffy. It means It is in the testing phase.

I also wanted to mention, with the age requirement, 50 to 85, a gentleman, Robert, from Sun Lakes, Arizona, wrote, and he's 88. If he is listening, since you are outside of the eligibility criteria, you could potentially be a recipient for Leqembi or ultimately, Kisunla. And the places in Arizona that you can access-- in Phoenix, Tucson and Sun City are the Banner Alzheimer's Institute or the Barrow Neurological Institute. So sorry for the digression, but I really wanted to help him out. So Nancy wrote, "What are the study sites?" And we have slides of them. Dr. Van Dyck, about how many total US sites are there and will there be?

DR. CHRISTOPHER VAN DYCK: Yeah. No, good question. Currently, we have 57 sites approved. Not all of them are active and in screening people yet. The majority of them are. And we're going to go a bit higher than that. And we're also actually going to be adding shortly a handful of Canadian sites, but we're in that range. The original goal was having 50 to 60 sites. I think we're going to go higher than 60, though.

NANCY LYNN: Oh, that's great. So for Nancy and anyone else who is interested in trying to see if there's a location near you, Alexa has put into the chat a link that you can find on the START study web page. It's basically find a location near you. And if you go to that link, you can see it in the chat, or you can always email us, and we'll give you this information again. Or you can just go on the START study website. And you put in your zip code. It will show you the nearest locations to you.

DR. CHRISTOPHER VAN DYCK: I can see questions in the chat. So I guess you're going to read those off, right? OK.

NANCY LYNN: Well, and people wrote into us. If you are what's commonly referred to as APOE4-positive, which is a sort of a genetic marker that makes you potentially more susceptible to getting Alzheimer's disease, early onset Alzheimer's disease, in particular, you would have one or two-- in this case, two APOE4 genes. And I wanted to ask you about that, which is the YouTube question from Lorraine. And also, someone wrote in, I believe Gloria, about-- let's see. Yeah. If this is applicable, potentially, in early onset Alzheimer's. She's from North Palm Beach, Florida. And she wrote, "My daughter, a former three-time Olympian, 57 years old, is far too young for this horrible disease. HELP," in capital letters. And so just looking at early onset and APOE4 or any other genetic condition.

DR. CHRISTOPHER VAN DYCK: Yeah. Well, first of all, for the age, as you already indicated, people can be as young as 50. So 57 is absolutely fine. Most people with early onset are perfectly good candidates for this. The exception would be the people who have those rare autosomal-dominant genes that run in some families. They're really quite rare-- account for less than 0.5% of everybody with Alzheimer's. But some of those people get onset in their 30s and younger even. So they're not suitable. But generally, early onset, Alzheimer's is perfectly fine. The question about APOE4 is

a really good one, and you alluded to people, Nancy, who carry APOE4 one versus two. But first of all, I mean, APOE4 is the major genetic risk factor for Alzheimer's disease. And in people who do have a symptomatic Alzheimer's, people have Alzheimer's, really, carrying one copy is very common. In fact, it's the majority. Probably, about 2/3 of people living with Alzheimer's carry APOE4. But mostly, it's just one copy. About 15% carry two copies, the so-called homozygotes. And I think the reason the question posed there is that it is known that for the plaque, the amyloid clearing drugs, like Leqembi or Kisunla, there is increased risk to people who are APOE44. So it's not so much with just one copy. It's the people who carry two. And frankly, many doctors prescribing Leqembi right now are not treating people who are APOE44 because of the increased risk, the side effects. But as a result of that, in the START study, we actually have a lot of people enrolling who are APOE44 precisely because they're not thought to be good candidates for Leqembi-Kisunla. And we are aware of no increased risk with CT1812 with a START study for people who are APOE44. The increased risk again relates to really eradicating, clearing out the plaques, which is also-- they're also in the blood vessels, not just in the brain tissue itself. And since this drug doesn't work that way, it doesn't appear to have such risks.

NANCY LYNN: Actually, I didn't realize that's fantastic for people who what they say are APOE4-positive or APOE44, that they can participate in this study, and that's fantastic. And John in the chat, you can see is noting that some clinical trials include a placebo group for half of the people participating or some percentage. Is that the case with this trial?

DR. CHRISTOPHER VAN DYCK: Yes. And I think many of you are aware to do a trial, to test a drug, you've got to have a control group. So the way it's set up in this case is 2/3 of people are on CT1812, 1/3 placebo. So it's not 1/2 and 1/2. The odds are in your favor of being on the active drug. And the 2/3 part, just to be clear, there are really three groups. There's a higher dose, a lower dose, and then there's the placebo group. And the two active doses-- one is 200 milligrams, one is 100 milligrams.

NANCY LYNN: When the study ends, will the placebo group potentially have access to go on drug if the results are favorable?

DR. CHRISTOPHER VAN DYCK: So, no, it's a great question. Right now,

there's no open-label extension planned. It's not part of the protocol. It does happen that sometimes during the trial, based on other information, sometimes the sponsor can make a decision, try to get extra funding, to add an extension. It could happen. I obviously can't promise that because it just isn't there yet. And sometimes, it's even a delayed thing, where they get all the results. And they say, yes, this is promising. And then they invite everybody back to then go on an open trial where everybody's getting the real thing. That's just not in effect yet.

NANCY LYNN: Not yet. All right. So we're going to be keeping our fingers crossed on that one. And I'm just happy to read this comment from Lorraine on YouTube. Thank you. I'm so excited to begin this trial. Go for it, Lorraine. And we hope you get in. And keep us posted if you do. And Holly asks, "What phase is this study?" It's a good question. And maybe you can give us like the super simple version of what the different phases of each trial are.

DR. CHRISTOPHER VAN DYCK: Yeah. First of all, this is phase two. There's phase one, two, and three, at least in the testing phases. And if a drug goes through all three of those, phase three. In the phase three, trials are positive. Then it's generally submitted for FDA approval. So phase one, all of these phases, they're not as clean as they may sound. But phase one usually starts with early safety and figuring out what dose is best. And it's based on, first, giving it to people with no disease, I mean, so-called normal controls. It can be just giving people single doses. They just take one pill. That's it. And they look at the levels in their blood. They look to see if they have any side effects. And then it goes to where people are dosed multiple for a period of time, usually just a month or so, where they get a daily dose for once a month. So really, the goals of phase one, I should emphasize, they're really about safety and trying to figure out the dose. Sometimes they look a little bit at other things, try to figure out if the drug is binding to what it's supposed to, but mainly safety and dosing.

And then in phase two, you get into what's called the "proof of concept." What does proof of concept mean? Well, it means that now, you're still looking at the safety and larger numbers of people, but you're also starting to take a look at benefit. And this drug has already been in some so-called

phase two studies. It's been in probably four or five of them already. But this one is the first that is actually big enough to really realistically ask the question, are people benefiting? Because this has 540 people, 180 in each of those three arms. And that is thought to be big enough. Well, the other thing I should really emphasize is the studies up until now have only treated people for no more than six months. And you can't see a whole lot in six months for a drug that's trying to modify the disease and really slow progression. So you really need about a year and a half, typically. And that's what this is-- year and a half, 18 months study. So this is the real proof of concept study to look at those things. And by the way, after this, this study would not be-- probably, however, let's hope that it's positive. If it is positive and shows statistically significant benefit to people, it's not going to lead to FDA approval right then and there because sometimes, it will be counted as a study, as one of the studies that will be reviewed for approval. But then they require the phase three's, also called "pivotal trials." Those are large. They can be 2,000 people, something more in that order. And those are really designed to ask the question, is this approvable?

NANCY LYNN: We have a couple of really interesting questions coming in. And the first is from Sue on YouTube. Can people who are on several other medications participate? And I'm going to imagine that during your intake questionnaire, they'll determine if whatever you're on is OK or not OK.

DR. CHRISTOPHER VAN DYCK: Yes. Yeah, that's a good question. And it's always a complicated question because in reality, we have massive lists of every drug there is about which are OK and which are not OK. But let me just say, the vast majority of things are fine. The number of things that are prohibited are relatively few. But there are some. It would be hard to go through all of them. But the kind of drugs that most people in this age group take like things for blood pressure, things for cholesterol, things for diabetes, those are all fine. They're more unusual things or are much less common things that could be prohibited. And that's exactly what we do. In the intake process, typically, a site will even do this over the telephone before somebody even comes in, just to ensure that there aren't any major obstacles.

NANCY LYNN: So that means, Sue, call him up. And this is a really, really interesting question as well. This is from Moira, and she says, "We were going to enroll in the HOPE study." And Dr. Van Dyck, we did the HOPE study--we profiled the HOPE study in one of our first episodes. And I assume you're familiar with that Cognito Therapeutics. And it is a sensory headset, I believe, with gamma waves. Moira asks, "Could we do both if the HOPE study allows it?"

DR. CHRISTOPHER VAN DYCK: So it's a great question. In general, a person can't do two investigational trials at the same time because--

NANCY LYNN: Because you don't know what is doing what.

DR. CHRISTOPHER VAN DYCK: Yeah, they're asking the same kinds of questions, especially when you think about benefit. If somebody's benefiting, well, what do they benefiting from? So you can't do them simultaneously. But you usually can do them in series. Like you complete one, you might have to go through a little bit of a gap in between, and then you can do another. And we've had people who did that kind of study, gamma oscillation. They have done that, and then they've gone on to do an actual medication trial.

NANCY LYNN: And Moira also asks, "Do the 24 visits have to be in-person?"

DR. CHRISTOPHER VAN DYCK: So this is a great question. Yeah, because that's a lot of visits. At the moment, they do. The thing that we're trying to amend is that in the beginning, in the first eight weeks, the visits are every two weeks. So that's really frequent. After that, they go to more like once a month. But in the first eight weeks, a lot of those visits are actually just for blood tests, and that's for monitoring the safety. So we're working on an amendment where somebody could go to a lab near them, like a Quest labs, that sort of thing. So they wouldn't have to come in for every one.

NANCY LYNN: Oh, that's great. So if Moira was interested at the time she inquires, she can find out where that stands, the ability to go to another lab.

DR. CHRISTOPHER VAN DYCK: Yes. Yeah.

NANCY LYNN: And I know this is a complex question, too, but we know that getting a diagnosis at exactly the right stage--mild cognitive impairment or early Alzheimer's dementia--is very difficult for people. A lot of primary care physicians will see somebody who really is at that stage, but doesn't really know enough about Alzheimer's and sends them home. And it's not fair for me to ask you this question. But we did get a question from Ken in Akron, Ohio, that is basically, how do if you're at the right stage? Because he says, my wife is about four to five years into late-term AD. We had an episode with Marwan Sabbagh about stages because people call these stages all different things. Sometimes there's nine stages. Sometimes there's three stages. So when Ken says late-term AD, and he's asking, he says, would this work for her? He says, she's now having trouble finding her words. And trouble word-finding, typically, is an is something you see earlier, at least in my mind, I'm thinking. So how do people really know if they're at the right stage? And what if they have been trying to get a diagnosis and haven't been able to? Can they still call and try to participate in this study?

DR. CHRISTOPHER VAN DYCK: Sure. Yeah. If somebody's not been evaluated, they don't have a diagnosis but they have symptoms, they're absolutely welcome to call. What we try to do is through the phone screening. What sites will try to do is through telephone screening, is figure out whether the person appears to be at the right stage. That's not foolproof. But we're not bad at estimating. One of the things is that people have often been seen and had like a standard test, like the mini-mental, the MMSE test, that 10-minute 30-point test, or the MoCA, another 30-point test. And if they've actually seen a doctor who's done those recently and they can share the scores, we can get a pretty good idea. By the way, the other entry requirement for this, when we say MCI or mild Alzheimer's dementia, it does have a mini-mental state score of somewhere between 20 and 30. So if they have a test of a mini-mental in a clinic and it's a 15, we really know that they're more in a moderate stage. Without that, though, we can ask questions like, I mean, start with, well, tell me about how they do dressing themselves. Can they pick out their clothes? Can they physically dress? And then you can go to harder things like cooking, managing their medications, even involved in personal finances, driving a car. I mean, people who do those things are clearly

mild. They're mild or MCI, Mild Cognitive Impairment. And they're almost certainly going to be good candidates. I mean, they may be too good for the study. They may not have evidence of anything sometimes. And we can only determine that if we see them and do the screening. But if somebody is not able to-- has trouble physically dressing themselves, they need assistance with bathing, with toileting, and so on, we know that they're going to be too impaired, just on the staging system, unless there's some other reason that they're not able to do those things. But the bottom line is, you should always feel comfortable calling the site, and they should do some screening. And when in doubt, come on in, and we'll see.

NANCY LYNN: Yep, you're looking to fill over 500 spots, so come on in and see.

DR. CHRISTOPHER VAN DYCK: Yeah.

NANCY LYNN: John asks, "Is there compensation for travel and participation in the trial?"

DR. CHRISTOPHER VAN DYCK: Yeah, it's a good question. Some of that is a little bit site-specific. Some sites have policies with their own review boards. But in general, people are compensated. It's not a lot. People aren't going to make money on this trial, but it's things like $50 per visit for, to offset travel costs. That would be very typical.

NANCY LYNN: Yeah. I also want to mention, because think about this a lot, that if you are in a placebo group, it's still very beneficial to participate in a trial because you are around the best scientists and the best investigators. And one way or another, ultimately, you will be getting better care than you would just being out there in the general universe. So I just wanted to put that in. And then I would be re-missed if I didn't talk about side effects. So I have a friend in the pharmaceutical industry who says, show me a drug with no side effects, and I'll show you a drug with no efficacy. And I don't know if you would agree with that, but what kinds of side effects would someone potentially expect from this drug?

DR. CHRISTOPHER VAN DYCK: Yeah, so great question. And I would say

this, just to keep this simple, in all of the testing to date, there's really one important side effect that has been identified, and that is that the drug can be associated with elevation, abnormal liver function tests. So those are very standard tests. And that is the reason that in the first eight weeks, we're doing those blood tests every two weeks, is for the liver function tests. Now, in terms of the frequency of those-- there are two doses-- 100 and 200. So far, it looks like people are on the 100 milligram don't have-- I mean, we have just haven't seen liver function abnormalities with the 100. The 200, probably there will be some. It's still early going for us in the trial. I should mention, we have 540 people. We've only enrolled about 50. So we got a long way to go.

And you could say, well, what would happen? I mean, with liver function test elevation, the important thing that a person doesn't get permanent damage to their liver. And that's why when the blood tests show elevation-- and by the way, many of you know, a lot of drugs that you take all the time, like statin drugs for cholesterol they're associated with the same thing. And when you start on one of those, your doctor's probably going to check liver function tests. But the important thing is to check, to monitor for it. And if they go up-- so there are two thresholds with this. If they go up a little bit, we say three times upper limit, then we pause the drug. We wait for them to go back to normal. And then we will probably try restarting the drug because there are many people who get a one-off elevation. And then upon restart, they don't get it again.

The other is, if they go higher than that and it happens to be five times upper limit, those people have to stop and not restart again. The risk is thought to be too high. And by the way, there have been no cases in all the testing to date of anybody having permanent liver damage. And I think the reason is precisely because we're monitoring quickly and intervening. And as far as what the percentage of people in the trial who might develop that, not sure. I think it will definitely be fewer than 5%. It may be lower than that. It may be lower than that because we're actually using a dose. 200 milligrams is actually lower than the dose that was used previously. It was 300. So we may find that we don't see very many at all. But that's the important thing. It's not to say that there's nobody who's ever had nausea or a headache related to this drug. And often, we don't even know if it's

the drug because those things are so common. It happens in the placebo group. So I would really say that the liver function monitoring is the most important thing.

NANCY LYNN: So it's really interesting because it seems to me there are many-- I want to say advantages, but I don't know if that's fair in this drug, in this treatment, as opposed to the infusion drugs that are available. The first being, obviously, that you don't have to go for an infusion. Many times, you're taking a pill. One is that you can participate if you're APOE4-positive.

DR. CHRISTOPHER VAN DYCK: And Nancy, let me clarify. APOE44 homozygote. So again, most people with Alzheimer's are APOE4-positive, and they can do Leqembi and Kisunla.

NANCY LYNN: Great.

DR. CHRISTOPHER VAN DYCK: Yeah, just to be clear.

NANCY LYNN: And there's no serious side effect like ARIA with which you find with Leqembi and Kisunla, even though those side effects are manageable. I'm very happy about those drugs becoming available. So I don't, in any way, mean to cast anything negative on them. But this is a very exciting trial to me, based on some of those items. Quick question. Will this work potentially, I know you're not testing it right now, but is there a possibility it could work in other dementias like frontotemporal dementia or Lewy body dementia or with Parkinson's and dementia or other types of conditions?

DR. CHRISTOPHER VAN DYCK: Yeah, wonderful question. Yeah, thank you for that. And the reality is this, that it's of interest for Lewy body dementia, and there's actually an ongoing trial in Lewy body dementia as well. Now, if somebody has a loved one with that and wants to know where, I actually don't know where the sites are. By the way, the drug is made by Cognition Therapeutics. That's the pharmaceutical company. And I should also just say, while I'm at it, this study is actually mainly sponsored by the National Institute on Aging, using our tax dollars. So this is being conducted by the academic consortium of all these university

sites around the country. But there is a pharmaceutical company partner who makes the drug. So it's really co-sponsored. And the Cognition Therapeutics website has information about the Lewy body trials. I don't know where the sites are offhand. But not frontotemporal dementia. There's been no thought that the mechanism would relate to that.

NANCY LYNN: And Parkinson's?

DR. CHRISTOPHER VAN DYCK: Well, if you mean idiopathic Parkinson's, common Parkinson's disease, no. I mean, Lewy body has an overlap of features of Parkinson's disease in Alzheimer's. So it has some of the Parkinson's pathology. So in that sense, yes, but not unless it's so-called dementia with Lewy bodies. And those are the people, just for those who don't know. They tend to have Parkinsonism-like rigidity, tremor, stooped, shuffling. A lot of them have visual hallucinations, very florid visual hallucinations, seeing animals, people, and so on. They tend to have something called REM behavior sleep disorder, where they act out dreams at night. And they also tend to have more fluctuation throughout the day and sometimes get a little overly sleepy in the daytime. So that's the condition where this is thought to be a potential benefit, and it's being tested.

NANCY LYNN: Someone wrote in and asked, and I'm not even sure if this is a fair question, since it's Cognition that you're working with. But what are the ingredients in the pill? They said, are they natural? Or are they chemical?

DR. CHRISTOPHER VAN DYCK: Well, I mean, CT1812 is a chemical. Let's be clear. It doesn't grow on trees somewhere. So I mean, I shouldn't say that glibly because there are drugs that do grow on trees. But no, this is very much a synthetic drug.

NANCY LYNN: And so if this drug proves to be effective and is approved, do you see a time where people will benefit from a cocktail of these drugs, where they're taking, once they're approved, not when they're in the testing phase. Will they enhance each other, potentially?

DR. CHRISTOPHER VAN DYCK: That's a wonderful question. Yes, yes,

yes. And I'll say, one of the reasons why, by the way, in this trial, we chose to allow people who are on Leqembi or Kisunla if they're stable, is that this drug, if it can't do something in addition to those drugs, it may not be clinically as relevant. So what we want to also be able to see is whether there's added benefit for somebody who's already on those drugs. Because I think in future, I think we envision somebody might be on an amyloid antibody. They might also be on a drug that affects the tau protein, a tau antibody, for example, and they might be on this drug. And they might still be on their Aricept. So, yes, I think we do envision so-called combination therapy or a cocktail approach.

NANCY LYNN: Well, I think this has been fascinating for me, I hope, and I think for everyone else. And I want to happily say that Lorraine, who's on YouTube, wrote, "I am scheduled to enroll on October 16."

DR. CHRISTOPHER VAN DYCK: I mean, she may not want to divulge this, but what site? Where does she live? I'm just curious to know.

NANCY LYNN: So, Lorraine, if you're interesting and you want to share that, put it into the chat, and we'll share that with Dr. Van Dyck. We can also share it with him privately, if you prefer. I want to thank everybody who participates in all of these Zoom Ins because we wanted people to be able to see each other and talk with each other and talk like this to each other. And I think that takes the shame out of the game and the isolation out of the game. And I hope we have more and more and more of these types of programs where people feel they can talk to scientists and knowledgeable doctors. So thank you, Dr. Van Dyck because there is, I think, a big divide between the scientific community and the general population. And also, personally, I believe there's a big divide between the scientific research community and doctors and nurses. So I'm going to wrap up, but we're getting a question. Folks are asking for your name and email. I don't know if you want to share that directly.

DR. CHRISTOPHER VAN DYCK: Yeah, sure. No, that's fine. I mean, it's publicly out there on a lot of things. I'm happy to have somebody email me. Let me just say one thing. I'm not able to do individual patient consultation in people I haven't seen. But in terms of answering questions about the study, the kinds of things we've been talking about, yeah, happy

to do that.

NANCY LYNN: Amanda, can you drop in the email into the chat, please? Thank you. And Lorraine is in Ohio. And I think, Lorraine, Dr. Van Dyck will be interested to know, as I am, which site you end up going to.

DR. CHRISTOPHER VAN DYCK: Yeah, I'm trying to remember. I know Case Western is a site. I'm trying to remember the other Ohio. I should know them all, but there are 57 and several recently added.

NANCY LYNN: And Moira, thank you. And Kelechi, thank you. Folks are very appreciative, Dr. Van Dyck, of this session. So before we say goodbye to Dr. Van Dyck, Roger, let me do some of our closing housekeeping. So here again is the website for the START study. It's start-study.org. And I think if you've participated before, you'll know that we have a lot of resources available on brightfocus.org. We have these free publications that we can send you in print or in digital. Understanding Alzheimer's Disease, Clinical Trials, a bunch of them, and more than are listed here. So if you would like copies of anything, call 855-345-6237, or you can email us at info@brightfocus.org. And the next slide. If you guys have trials that you're interested in learning more about or subjects, in general, on Alzheimer's, please suggest topics at reply@brightfocus.org. And the next slide. Oh, that's really interesting. Kelechi ask this in a minute.

I just want to let everybody know we have an amazing guest on October 17, Dr. David Holtzman. And we're going back to the question of "How Is Dementia Diagnosed?" Dave's partner, Randy Bateman, did an episode on this subject about a year ago, and there has been so many developments in the field that we felt it's necessary to do it again. And it was also the highest--over 50,000 people viewed that episode to date. So Thursday, October 17, 1:00 Eastern, 10am Pacific. How Is Dementia Diagnosed?

And before we leave, Dr. Van Dyck, Kelechi wrote, "I'm a PhD student in Neuroscience and Neurodegenerative Disease. Is there any way I can participate or assist in this study? I stay in San Antonio, UT Health, San Antonio. So we can also let you guys chat privately.

DR. CHRISTOPHER VAN DYCK: Sure. Well, I know there's a site in San

Antonio, Dr. Arash Salardini. So I mean, this person may be able to contact Dr. Salardini.

NANCY LYNN: So Kelechi, if you want to do that, go ahead and do that directly. If you need me to make any connections for you, you can email to us at reply@brightfocus.org, and I will connect you. So Dr. Van Dyck, thank you so much for participating today. I think this was a great session. I hope lots of people join your trial, and I hope that we're going to have you back 20 months from now, telling us how well this drug has performed. And thank you for a career dedicated to people with dementia. Really appreciate it.

DR. CHRISTOPHER VAN DYCK: Thank you, Nancy.

NANCY LYNN: My pleasure.

DR. CHRISTOPHER VAN DYCK: Thank you. And thanks to everybody for attending today.

NANCY LYNN: Yeah, thank you all for attending. Hope we'll see you on October 17. Be well. Have a great day.

Resources

- The START Study - https://START-study.org or call 1-833-START-33 (1-833-782-7833)