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So the first question here is actually geared towards Dr. Richard Hodes, though I think, with the framing of the question, there might be a few other colleagues that could chime in, as well. So Dr. Hodes, we will start with you. What does this mean for the amyloid hypothesis? You mentioned other targets and markers. Could this trial be used as a blueprint to test drugs that are aimed at other targets in Alzheimer's prevention? Now, this is from Richard Staines from BioWorld.

Thank you for the question. So to the aspect of the question that asked whether this could be a model for various approaches to prevention, the answer is very much yes. As I alluded to, the combined ability to identify individuals at high risk by genetic but by other parameters, as well, a relatively recent accomplishment, together with the availability of biomarkers, both imaging and the fluid or blood biomarkers that we referred to, does provide a paradigm for rigorous randomized controlled trials to look at the ability to prevent, as well as treat.

I would emphasize again the importance of looking at a multiplicity of targets. And in fact, in many individuals it may be there will be differences in the pathogenic mechanisms. That is, the underlying molecular mechanisms that will need to be treated. As far as the amyloid hypothesis, I think what we have learned progressively has led us to think that our best opportunity to intervene successfully has been to move to earlier stages before damage, potentially irreversible damage, has been done. This prevention trial is an example. And there are those under design and execution which will continue to move to even earlier stages.

There also be a combination of agents used. This is one antibody in the current study that was used, designed, identified for very rational and appropriate reasons, but there are others that target various forms of amyloid. So we will be committed, I'm sure with all of our partners, to looking with this paradigm for prevention research, looking at a multiplicity of targets. Right now, just for example, for those that are supported by NIA-- and this is only a subset-- there are some 69 pharmacologic studies ongoing. The more advanced of those, late-stage, II, III, are about 50% targeted in amyloid, 50% otherwise.

Of the 61 that are earlier-stage trials, the majority, some 3/4, are addressed to targets other than amyloid. So amyloid remains an important target, potentially in addition to or in combination with others. I'd note there are also nonpharmacologic interventions that are as legitimate as part of our armamentarium currently being addressed. So I hope that addressed the questions. Be happy to elaborate further. And as noted, this is a relevant question to all of my colleagues here on the call, too, if anyone else would like to respond.

Thank you, Dr. Hodes. So Annalee Armstrong from Fierce Biotech. Dr. Doody, I believe we'll start with you for this one. Do you see any read-through data from today's outcome to your other amyloid therapy, gantenerumab, which is expected to read out late this year?

Yes. You know, every study is carefully designed to ask the questions it's asking. This was a study of people with a genetic form of Alzheimer's disease treated very early, before there were clinical symptoms, and sometimes before amyloid, with a particular monoclonal antibody that was designed in a particular way to target oligomeric beta-amyloid.

That is completely different than other studies underway with other molecules, including one of ours that was asked about, which is a monoclonal antibody, gantenerumab, directed against fibrillar and deposited a-beta, and is currently under study in two global phase III trials of 1,000 patients each, expected to read out at the end of this year. So different patients, sporadic Alzheimer's disease, patients with prodromal to mild, meaning MCI and Alzheimer's disease in a mild form, different design, different analysis, and different molecules. So I think we really can't read across from one molecule to another.

Thank you, Dr. Doody. We'll actually stick with you for a continuation of one of Annalee's questions, and then maybe over to Dr. Hodes. Can you please summarize what this means for the early intervention theory in Alzheimer's disease? And will you continue to explore the idea that treating early in the disease could be the key to preventing cognitive decline?

Yes. You know, I think it's very important, something that I alluded to a moment ago. We really need to treat Alzheimer's disease whenever it occurs. And no matter what we do as human beings, there will probably not be complete prevention in everyone. So I think we need to think broadly about our therapeutic approaches. Prevention should certainly be foremost. And we have learned a great deal from this study, as well as other studies that all of us have participated in that have a primary or a secondary prevention approach.

So prevention is very much alive. It needs to be one of our targeted therapeutic approaches, but probably not our only one. And many things were learned from this trial and will continue to be learned from this trial. As mentioned, there were some differences between the treated and untreated patients. We still need to understand which patients were most likely to experience those differences. We need to understand the biomarkers involved and what it's telling us about the disease and the timing of the intervention. So prevention is very much a part of the program for the future, but not the only one.

Thank you, Dr. Doody. Dr. Reiman, would you have some comments to extend on that?

Thank you, Jen. When we first designed this study, we thought there was the potential for treatments to have a more profound effect if started early in the disease, before the people become impaired and the disease is already extensive, be able to detect an effect. And we thought that this study could provide a better test of the particular treatment in these individuals than in impaired individuals.

That said, while we were not able to see a clinical effect with this drug, it doesn't rule out the possibility of seeing a clinical effect with other anti-amyloid treatments. And we don't yet know the extent to which we've engaged the target oligomers because we don't have great assays. We do not yet know the effects we may have had on higher doses. For these and other reasons, the amyloid hypothesis still needs to be tested. And that test will necessarily include additional prevention trials in groups just like this one.

Thank you, Dr. Reiman. We have a question for Dr. Pierre Tariot from Gabrielle at ALS Forum. Which of the secondary and exploratory biomarker showed numeric trends?

Thanks for the question, Gabrielle. We will be presenting those details at the Alzheimer's Association International Conference on August 2nd.

Thank you, Dr. Tariot. A reminder to all in attendance, we are still open for questions. As of right now, I will actually ask Dr. Tariot if you could explore just a little further on what hope you have that this further analysis of the data-- excuse me-- data might reveal of some of the positive news.

But it's frankly too soon for me to give a temperature read. The data lock that just occurred very recently. You're getting news hot off the press. There are numerous analyses ongoing. There are numerous analyses that haven't been launched yet. So we'll be able to give you all a much richer picture of the trial results. As I said, or tried to say before, this is the beginning of the story, but by no means the end of it.

Wonderful. Thank you so much. Gabrielle from ALS Forum. In the DIAN trial-- and forgive me, I cannot pronounce this drug name on this one-- Dr. Reiman, can you explain how the drug showed a trend toward worsening on some outcomes, which was puzzling. Did you see any indications disfavoring crenezumab or any of the outcomes?

You know, Jen, since the drug that was studied in that regard was from Roche, gantenerumab, perhaps Rachelle Doody could just comment on that.

Drugs studied in the DIAN trial. One was solanezumab. And that is the one that I think the questioner may be asking about because there were some biomarker trends toward worsening, but of no clear clinical significance at all with solanezumab. Gantenerumab was another arm in the study. Now, that was a different kind of prevention trial because all of those patients were symptomatic.

So it was a later stage than this particular study, the API trial that we're talking about today. Gantenerumab patients also did not show a clinical benefit, but they showed downstream biomarker changes. And so we're seeing in the field that we have to push a lot of AD pathology out of the way, but then we often begin to see a glimmer of differences, whether that is in biomarkers of disease pathology or even in clinical measures with very small differences. We're seeing this in a number of different settings.

And Jen [INAUDIBLE] it's Pierre Tariot, if I may build off what Dr. Doody just said?

Yes, absolutely.

Dr. Doody, you may want to comment on whether-- about the continuation of gantenerumab treatment in that paradigm. But there was an aspect to the question as I heard it of whether there was evidence of reverse efficacy with crenezumab. And the answer is absolutely not. But Dr. Doody, I don't know if you want to comment any further on gantenerumab in DIAN.

I think, really off the topic of today's discussion, but there are some papers out there and additional things coming out all the time about that particular prevention study. We also have a secondary prevention study in sporadic Alzheimer's disease underway with gantenerumab.

Great. Thank you. Dr. Reiman, we have a question from Gary Stix from Scientific American. I believe you will be able to probably share this response with a few colleagues, so please include them as you feel appropriate. Did this trial provide any insight into the biological processes involved in the presymptomatic stages of Alzheimer's disease? And will it enable the development of new approaches to biomarkers?

Thank you for asking that question, Gary. This study is going to provide invaluable information to informing us about the biological and cognitive changes associated with the earliest detection and tracking of Alzheimer's disease in these frequently assessed mutation carriers and non-carriers over five to eight years. In the placebo group, that information is going to help and further inform the design of secondary and primary prevention trials so that we can optimize the cognitive measures that could be used in further studies and increase the power to test treatments in those who already have amyloid plaques on board, and also to understand the biological changes in amyloid-negative individuals who are about to develop amyloid plaques to see if we can begin to use those biomarker changes to advance the evaluation of primary prevention therapies.

We think this shared data is going to be extremely important in that regard. And we also think we're going to have some learnings from the effects of treatment. Just to remind you, this study included not only a range of cognitive measurements, it included amyloid PET, later in the study, the introduction of tau PET, a range of MRI measurements, cerebrospinal fluid measurements in many of the participants, and the opportunity to look at annual assessments of these biomarkers with blood in a group that we have annual measurements in every single participant. We think we're going to learn an awful lot from this information and it will further accelerate the evaluation of prevention therapies.

Thank you, Dr. Reiman.