Thank you, everyone, for joining us for today's media briefing on the Alzheimer's Prevention Initiative, Autosomal Dominant Alzheimer's Disease or ADAD trial. My name is Jen Fenter, a Public Relations Director at Banner Health, and I will be moderating for today. Please note this media briefing is live and it is being recorded.

Today you will hear from a variety of speakers to ensure you have the context and information from each of the crucial contributors from the API ADAD trial. I'd like to start by briefly introducing them to you and the perspectives they plan to discuss. Dr. Eric Reiman is Banner Alzheimer's Institute Executive Director and one of the study's leaders. He will provide background on the strategic aims of the Alzheimer's Prevention Initiative as well as highlight the overall goals and significance to the field from the API ADAD trial in particular.

Dr. Pierre Tariot is the Director at Banner Alzheimer's Institute and another study leader. He will be speaking to the trial design and initial endpoint results that were released earlier today. He will also explain some of the additional data that is still being reviewed and will be made available at the Alzheimer's Association International Conference later this summer.

Dr. Francisco Lopera is joining us from Colombia. He is the Neurosciences Research Director at the University of Antioquia. He will discuss the partnership between the University and the families in Colombia who have volunteered to participate in the trial as well as the impact of the trial on these families and next steps.

Dr. Richard Hodes is the Director at the National Institute on Aging at the National Institutes of Health, the primary US federal agency supporting and conducting Alzheimer's disease research. He will provide context from the federal government's viewpoint. And last but not least, we have Dr. Rachelle Doody. She is the global head of neurodegeneration at Roche and Genentech and will highlight the importance of public private partnerships and what learnings are from pioneering studies like this one.

Now, before I hand this over to our speakers, I do want to mention a few things to make this briefing successful for everyone. If you have any questions at any time during this briefing, please chat them into the Q&A box at the top right of your screen. If you don't see the chat box, please click on the question mark icon in the navigation bar. Please make sure you include your name and media outlet affiliation with your question. Now, please try and remember to type your questions as if you're asking it in person so I can read them clearly to our appropriate expert.

After this press conference concludes, we will provide you with the high resolution recording to be used for your stories that will post to our newsroom. This will include a transcript and supporting materials. You will find it within the next two hours over at bannerhealth.com/newsroom. Without further delay, I'd like to introduce you to our first speaker, Dr. Eric Reiman.

Thank you, Jen. Earlier today we announced topline findings from the groundbreaking Alzheimer's Prevention Initiative Autosomal Dominant Alzheimer's Disease prevention trial, which was conducted in Antioquia, Colombia. Sadly, the investigational therapy crenezumab did not significantly slow down, delay, or prevent thinking or memory declines in cognitively unimpaired mutation carriers from the world's largest autosomal dominant Alzheimer's kindred. While estimated mean annual changes in our co-primary endpoints and multiple secondary and exploratory endpoints favored crenezumab over placebo, none of these results were statistically significant. My colleague Dr. Pierre Tariot will discuss the findings further in a few minutes.

Since we were required to announce our topline findings as soon as possible, we need a little bit more time to review our current results and complete potentially important additional analyses. For instance, we still need to explore crenezumab's clinical and biomarker effects in the mutation carriers who did or did not yet have PET evidence of amyloid plaques when they entered the trial. Since many of the mutation carriers did not yet have measurable amyloid plaques at the time, there's a chance to characterize and compare the effects of treatment in the so-called secondary versus primary prevention of Alzheimer's disease.

In addition, in this study over time, the dose of the drug was increased dramatically to maximize the potential for a therapeutic effect. And more work needs to be done to understand the impact of dose and duration on our findings. Our findings will be presented at the Alzheimer's Association International Conference in August, and additional findings will be presented later this year.

We're disappointed that crenezumab did not show a significant clinical benefit. Our hearts go out to the families in Colombia and to everyone else who would benefit from an effective Alzheimer's prevention therapy as soon as possible. At the same time, we take heart in the knowledge that this study launched and continues to help shape a new era in Alzheimer's prevention research.

When the API ADAD prevention trial was announced at the first NIH Alzheimer's Disease Summit in 2012, the NIH director called the trial a cornerstone in the national plan to address Alzheimer's disease and he considered the grant a down payment on what would become a remarkable bipartisan national investment in Alzheimer's disease research and care that has transformed the fight against Alzheimer's disease. Scientific American designated the trial as one of its world changing ideas of the year.

Before we got started, there were no Alzheimer's prevention trials of promising drugs, no clear way to accelerate the evaluation and approval of effective prevention therapies, and no clear plan to make that happen. There was no commitment to share data and samples from each other's clinical trials and there was no sense of urgency among different stakeholders about how to find effective Alzheimer's prevention therapies as soon as possible. All that has changed.

The announced trial showed that Alzheimer's prevention trials were possible. It introduced groundbreaking research strategies and methods that have helped shape Alzheimer's prevention research, led to a growing number of prevention trials in cognitively unimpaired persons at biological risk for the disease, and sped up the effort to find effective prevention therapies and support their potential approval as soon as we can.

And established a precedent setting commitment to the sharing of trial data and samples with the field in order to have the greatest possible impact, a commitment that was embraced and enhanced in collaboration with other prevention programs. And it has promoted dialogue and a shared commitment to Alzheimer's prevention among a wide range of stakeholder groups. There are now a growing number of ongoing prevention trials. There are more to come, and we feel privileged to be part of it.

Despite today's disappointing news, the preparation, performance, and completion of this trial was a monumental achievement made possible with our support by Dr. Francisco Lopera and his remarkable neurosciences group at the University of Antioquia, more commonly known as GNA. For instance, GNA identified and enrolled 6,000 members of this autosomal dominant kindred in the Alzheimer's Prevention Initiative ADAD prevention registry all descended from the same ancestor. And it included nearly 1,200 individuals who carry this Alzheimer's causing mutation.

GNA established the clinical trials, PET, MRI, and infusion infrastructure needed to conduct the study, worked at rural and central locations, and completed the trial in extremely productive and responsible ways. It worked closely with the families, engaged them in the fight against Alzheimer's disease, providing a model of how to conduct a first of its kind prevention trial of an experimental drug in a vulnerable population from a developing country and do so in a way that's highly valued by the participants themselves. Despite the distances some of the participants traveled, the numerous procedures that they endured, occasional travel restrictions due to civil unrest, and the COVID pandemic, 94% of the participants completed this five to eight year trial. Amazing.

In addition to GNA, we've had the great fortune to work with our partners from Genentech and its parent organization, Roche. They embraced this study and our ambitious goals from the start. They set an example that other companies have followed by their investment in Alzheimer's prevention research, and they continue to provide invaluable scientific, regulatory, and operational input, guidance, and support.

From the beginning, the National Institute on Aging has been a wonderful partner. Their thoughtfulness, understanding, and support have been remarkable. There are so many people who have contributed to this study in the planning, performance, and analysis stages, and we're grateful to all of them. I'm particularly grateful to Banner Health, Banner Alzheimer's Foundation, and our extremely generous philanthropic donors for all they did to make this study and the initiation of this new era in Alzheimer's prevention research possible.

I want to take a moment to speak directly to our incredible research participants and families in Colombia. My Banner colleagues and I want you to know that we're not going anywhere. We have heard you loud and clear about your determination to help find an effective prevention therapy for your families and other families around the world, and we plan to be there with you to support that goal every step along the way.

While we're disappointed that crenezumab did not show a significant clinical benefit, we remain excited about the future of Alzheimer's prevention research inside Colombia and around the world. We expect our shared data samples and findings will further accelerate the evaluation and potential approval of primary and secondary Alzheimer's prevention therapies. We retain the hope that one of our ongoing prevention trials will find and support the approval and availability of an effective Alzheimer's prevention therapy within the next few years. The API Autosomal Dominant Alzheimer's Disease trial has played a fundamental role in that endeavor. Now I'd like to introduce you to my colleague, Dr. Pierre Tariot. Pierre.

Internist, geriatric psychiatrist, and clinical trialist. And together with Jessica Langbaum, Dr. Jessica Langbaum, Dr. Robert Alexander, Dr. Reiman, one of the principals of the Alzheimer's Prevention Initiative broadly and specifically in Colombia in partnership with Dr. Francisco Lopera and his team. So you've heard the key points. Let me just fill in a few details here.

So this was a prospective randomized double blind placebo controlled parallel group potentially label enabling or supporting phase II trial. It investigated the efficacy of the monoclonal antibody crenezumab versus placebo in cognitively unimpaired individuals who carry the presenilin-1 E280A autosomal dominant mutation. In fact, the trial also included a cohort of mutation non-carriers because the community standard at the time was not to require genetic disclosures. So this was in essence a two part study, a placebo controlled trial of crenezumab in mutation carriers and a cohort study of mutation carriers and non-carriers receiving placebo.

The participants who were mutation carriers were randomized to crenezumab or placebo for at least 260 weeks up to a maximum of 416 weeks. We sometimes refer to this as a common closed design whereby the first person enrolled and the last person enrolled have their final efficacy visits at about the same time. The dose of crenezumab was escalated at different points over the course of the trial based on external data. And I believe Dr. Doody will tell you quite a bit more about the molecule and the dosing issues. But as Dr. Reiman hinted, this can be an important part of the analysis.

The consequence is as we learned more from the field that perhaps higher and higher doses would be advantageous, the maximal dose was not delivered for the entire treatment period. And the most people received the highest dose was for about two years. The efficacy of crenezumab was assessed according to two primary outcomes, change in overall cognitive function and change in memory function. These are clinical manifestations of emerging Alzheimer's disease.

Specifically the overall cognitive measure was the annualized rate of change in the API Autosomal Dominant Alzheimer's Disease composite cognitive test score, which is empirically derived from longitudinal studies in this population. The study of the measure of episodic memory was the annual rate of change in the free and cued selective reminding task cueing index.

You heard about the remarkable registry that the neurosciences group created with thousands of people. From that, the study enrolled and randomized 252 participants, including 169 preclinical mutation carriers and an additional control group of 83 mutation non-carriers from the same family kindred. Again, they were included to mask mutation carrier status. In terms of results, you've heard the headline. We did not demonstrate a statistically significant clinical benefit in either of the two co-primary or really dual out points. By that I mean there would have been a potential win if either one or both showed a drug placebo difference.

Importantly, there were no new safety issues identified with crenezumab during the study. The further initial clinical brain imaging and CSF biomarker results will be shared at the Alzheimer's Association International Conference taking place July 31st to August 4th in San Diego. And then subsequently, additional data, including results from blood based biomarker findings, will be shared as they become available.

Those are the main points I wanted to bring up. And now I'd like to introduce you to our esteemed colleague, Dr. Francisco Lopera, who is the Research Director of the Neurosciences Group at the University of Antioquia. Dr. Lopera.