DIAN-TU Alzheimer's prevention trial opens enrollment to third drug

Effort to study drug's ability to prevent, delay the disease

Editor's note: This information was updated Aug. 19, 2017, to reflect that patients can now enroll in the third drug arm of the trial and that Cerveau Technologies has provided an investigational imaging-based marker that is being evaluated as part of the study.

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Washington University School of Medicine's Randall J. Bateman, MD, talks with DIAN-TU trial participant Natalie Shriver, of Omaha, about a study to test drugs that may prevent or delay Alzheimer's disease.

An international team led by the DIAN-TU at Washington University School of Medicine in St. Louis is now enrolling patients in the third investigational drug arm of a worldwide clinical trial that is evaluating whether oral medications can prevent Alzheimer's disease.

Participants for the study will come from families with a Dominantly Inherited Alzheimer's Disease mutation. Potentially eligible participants can request information at the Dominantly Inherited Alzheimer Network Expanded Registry, www.dianexr.org.

The third drug, originated by Shionogi & Co., Ltd., in Osaka, Japan, is being developed by Janssen Research & Development, LLC, in New Jersey. It is designed to lower the production of amyloid beta, a protein that clumps together into plaques and damages neurons in the brain, leading to memory loss, cognitive problems and confusion. The drug is designed to block the enzyme beta secretase — which produces amyloid beta — with a goal of reducing the amount of amyloid beta available to clump and cause neurodegeneration. This mechanism is designed to block the effects of mutations, which increase forms of amyloid beta.

This investigational drug joins two others already being evaluated in the Dominantly Inherited Alzheimer Network Trial Unit (DIAN-TU) study, which involves people with an inherited predisposition to develop Alzheimer's at a young age, usually in their 30s, 40s or 50s. Participants already enrolled will continue on their existing drug regimens, and additional volunteers with no or mild symptoms of cognitive impairment will be enrolled to evaluate the third drug.

"We are delighted with the new collaboration with Janssen Research & Development to expand the number of novel therapeutic targets we are testing," said Washington University Alzheimer's specialist Randall J. Bateman, MD, Director of the DIAN-TU. "Testing a beta secretase inhibitor in the DIAN-TU trial further diversifies the approach to speed the identification of preventions and treatments for this devastating disease," added Bateman, who is also the Charles F. and Joanne Knight Distinguished Professor of Neurology at Washington University.

The DIAN-TU is a public/private philanthropic research partnership that launched the trial in 2012. It is the first trial aimed at identifying drugs to prevent or slow Alzheimer's in people who are nearly certain to develop the disease due to inherited genetic mutations. Specifically, people in the trial are at risk of having mutations in one of three genes – *APP*, *PSEN-1*or *PSEN-2* – which are linked to early-onset Alzheimer's. The hope is that by intervening early – before Alzheimer's ravages the brain – it may be possible to thwart the disease.

As part of the trial, three-quarters of new enrollees will be randomly assigned to receive the beta secretase inhibitor, and one-quarter will receive the placebo. Both groups will be evaluated for at least four years to determine whether the investigational drug delays or prevents the onset of Alzheimer's disease.

"Janssen welcomes this opportunity for researchers to test the mechanism of beta secretase inhibition in people who have dominantly inherited genetic mutations that put them at substantial risk of early-onset Alzheimer's disease. The DIAN-TU trials will provide a rigorous and powerful test of the amyloid hypothesis while evaluating a potential preventive treatment option for autosomal dominant Alzheimer's disease," said Gary Romano, MD, PhD, the head of Alzheimer's Disease Development for Janssen Research & Development.

Although the trial focuses on people with rare mutations, treatments that are successful in this population potentially could be used to slow or stop the forms of Alzheimer's that occur more commonly in older adults. It is thought that the destructive molecular and cellular processes in the brain are much the same for both types of the disease.

"We are pleased to see the DIAN-TU trial researchers continuing to broaden the types of investigational drugs they are testing," said Maria Carrillo, PhD, chief science officer of the Alzheimer's Association, which is helping to fund the trial. "Alzheimer's is a very complex disease, and it is extremely important that we develop therapies to address Alzheimer's from a variety of angles and at multiple stages of the disease."

Along with beginning testing of the beta secretase inhibitor, the new arm of the DIAN-TU study uses a new disease progression model to identify changes in cognition earlier and includes more frequent cognitive testing using remote applications.

In addition, the trial will include an investigational imaging-based marker targeting disease progression. This novel radiopharmaceutical tracer – which is being developed by Cerveau Technologies and called [18F]MK-6240 – is designed to detect brain protein tau levels by positron emission tomography (PET) scan. Tau accumulates in the brain where it forms toxic tangles in individuals with Alzheimer's, and has been shown to be tightly linked with the symptoms of loss of memory and thinking. By tracking the tau tangles in the trial, the DIAN-TU may help validate this marker as a short-cut to drug development.

"Cerveau is excited to be working with Dr. Bateman and his colleagues at DIAN-TU to help fight Alzheimer's disease and to better understand tau pathology," said Rick Hiatt, President and CEO of Cerveau Technologies, Inc., "The partnership with DIAN-TU is another important step forward in our strategy of developing and supporting an international network of key collaborators and production sites to enable broad access for scientific research and clinical trial support."

The DIAN-TU trial is ongoing at 24 sites across seven countries. Because of the rarity of individuals that have a dominantly inherited Alzheimer's disease genetic mutation, the program will be expanded to additional countries, potentially including Argentina, Brazil, China, Colombia, Germany, Hong Kong, Ireland, Japan, Korea, Mexico, Netherlands and Poland.

The DIAN-TU is a public-private partnership of academic centers, the Alzheimer's Association, the U.S. National Institute on Aging (NIA) at NIH, Eli Lilly and Company, Roche and Janssen Research and Development. Other supporters include GHR Foundation, Fidelity Biosciences Research Initiative, Accelerating Medicines Partnership, Cerveau Technologies, Avid Radiopharmaceuticals, Cogstate, Bracket, and the DIAN-TU Pharma Consortium (members include AbbVie, Amgen, AstraZeneca, Biogen, Eisai, Janssen/J&J, Eli Lilly & Co., Pfizer, Roche and Sanofi).

"This is a very exciting and innovative collaboration in Alzheimer's disease research," says Richard Hodes, M.D., NIA director. "Not only are the government, foundations, advocates and companies involved, but a most important component of this trial is the active and informed participation by families so deeply affected, whose contributions will tell us a great deal about this disease and how to attack it."

For people with Alzheimer's, family members, doctors and researchers interested in participating, the DIAN-TU launched the DIAN Expanded Registry (DIAN EXR). For more information or to register for potential participation in the trial, go to www.dianexr.org, call 1-844-DIAN-EXR (342-6397) or email dianexr@wustl.edu.