

DIAN EXR Newsletter

Volume 6, Issue 1, 2024

A newsletter distributed by the Dominantly Inherited Alzheimer Network Expanded Registry (DIAN EXR),
Washington University School of Medicine
Department of Neurology



Washington
University in St. Louis

SCHOOL OF MEDICINE

2024: New Year, New Trial Announcements

Nearly midway through 2024, we're catching our breath long enough to share some exciting developments: the most exciting being updates on two clinical trial endeavors. As detailed in the following pages, The Knight Family DIAN-TU Amyloid Removal Trial (ART) will continue monitoring DIAN-

TU-001 gant OLE participants, resulting in long-range data from this unique cohort of participants. In addition, the DIAN-TU-002 Primary Prevention trial will resume its study of participants who are 11 to 25 years younger than their anticipated age of symptom onset.

The trio of research efforts—the DIAN Trials Unit, DIAN Observational Study, and DIAN Expanded Registry—is unique in its commitment to ongoing conversation with research participants. On May 4, 2024, webinars with prospective ART and Primary Prevention participants allowed these individuals direct access to DIAN-TU investigators, to ask questions and share concerns. These conversations shape communications and inform future trial design.

It can feel like a cliché to describe research as a partnership—yet partnership is the goal of DIAN and DIAN-TU research. As those of us in the northern hemisphere move into the summer months, we look forward to conference gatherings with both DIAD families and scientific partners, as well as upcoming trial protocol announcements and enrollment

timelines. We look forward to continuing these new endeavors—together!

The Knight Family DIAN-TU-003 Amyloid Removal Trial

As previously announced by the DIAN-TU on 18 December 2023 and the Alzheimer's Association on 09 April 2024, the Knight Family Dominantly Inherited Alzheimer Disease Trials Unit (DIAN-TU) is launching the DIAN-TU-003 Amyloid Removal Trial (ART) to enable continued treatment for the DIAN-TU-001 Gantenerumab Open Label Extension (OLE) participants and address questions regarding the effects of removing amyloid plaques to normal levels on cognitive symptoms, clinical progression and disease processes. The DIAN-TU-003 ART is an important study for the field of Alzheimer's disease (AD) with the potential to answer key scientific questions regarding drug dose and duration, mechanism of action, safety, and optimal timing, exposure and effects of treatment to provide the greatest clinical benefit. DIAN-TU-001 OLE

participants were treated with the anti-amyloid therapy gantenerumab for 2 to 10 years, representing the longest treated group of patients with amyloid removing antibodies. Findings show that for this group of participants, overall, there was partial but not full amyloid removal. The DIAN-TU-003 ART will enable continued evaluation of the long-term effects of amyloid removal on disease progression in these participants and may provide important information regarding whether removing amyloid plaques can delay, slow, or prevent symptom onset and clinical progression in dominantly inherited Alzheimer's disease (DIAD).

Trial Design

The DIAN-TU-003 ART is an open-label study to treat DIAN-TU-001 OLE participants with lecanemab for a minimum of 5 years, utilizing a common close design. Lecanemab is an anti-amyloid monoclonal antibody passive immunotherapy which demonstrated robust amyloid removal capabilities and clinical efficacy in early-stage symptomatic AD. Currently available clinical trial data suggest that, with monitoring and management, lecanemab treatment has acceptable safety and is generally well tolerated. Participants will

be co-enrolled in the Dominantly Inherited Alzheimer Network Observational (DIAN Obs) natural history study (NCT00869817) through which clinical, cognitive, imaging and fluid biomarker assessments will be conducted. The main objectives of the 5-year DIAN-TU-003 ART are:

- To determine the effects of amyloid removal on age of onset and clinical progression
- To determine if amyloid plaque can be fully removed in DIAD
- To determine the effects of amyloid removal on biomarkers of disease progression

... The DIAN-TU-003 ART is targeted to launch by the end of Q2 – early Q3 2024 in the United States and by the end of 2024 in the United Kingdom, Europe, and Australia.

Eligible participants will be contacted by DIAN-TU-001 OLE study coordinators to assess interest; however, you may also reach out to your site Principal Investigator, study coordinator or the DIAN Expanded Registry (DIAN EXR) at dianexr@wustl.edu for more information. If you are not already registered with the

DIAN EXR, please consider enrolling by visiting dian.wustl.edu. DIAN EXR participants receive the most up-to-date information via email blasts, newsletters and webinars with DIAN-TU directors.

For full details, visit <https://dian.wustl.edu/the-knight-family-dian-tu-003-amyloid-removal-trial/>.

The Knight Family DIAN-TU Primary Prevention Trial Announcement

The statement below is an update to the 20 December 2022 announcement by the Knight Family Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) regarding the DIAN-TU-002 Primary Prevention Trial.

In late 2022, the Knight Family DIAN-TU paused the launch of the DIAN-TU-002 Primary Prevention Trial of gantenerumab due to discontinuation of the drug development program. We are now pleased to announce plans to re-launch the DIAN-TU-002

Primary Prevention Trial with remternetug in collaboration with Eli Lilly and Company (Lilly).

Remternetug is an investigational monoclonal antibody developed by Lilly that targets and removes amyloid plaque in the brain. Other amyloid targeting therapies with similar activity have been found to slow the progression of cognitive and functional decline in individuals with symptomatic, non-autosomal dominant, Alzheimer's disease.

Remternetug can be administered subcutaneously, potentially offering a convenient treatment option to patients across the AD spectrum.

“We are extremely pleased to resume the DIAN-TU-002 Primary Prevention trial in partnership with Lilly”, said Eric McDade, DO, a professor of neurology at Washington University and the trial's principal investigator. “Since the pause of the Primary Prevention trial, there has been clear demonstration of clinical benefit from amyloid lowering therapies at the symptomatic stage of Alzheimer's disease. This only strengthens our need to resume the first true prevention study in Dominantly Inherited Alzheimer

disease targeting amyloid pathology at the earliest possible stage.”

Unlike historical Alzheimer’s disease trials, the DIAN-TU-002 Primary Prevention Trial will treat individuals prior to onset of significant amyloid plaque build-up in the brain-up to 25 years before the expected onset of dementia. Results from recent trials and FDA approved drugs for Alzheimer’s disease have demonstrated the benefit of removing amyloid plaques from the brain. This trial will demonstrate whether remternetug can prevent amyloid plaque accumulation in participants with dominantly inherited Alzheimer’s disease (DIAD), and if prevention of amyloid build-up in DIAD can prevent or substantially slow this form of the disease.

The DIAN-TU-002 Primary Prevention Trial will utilize the current network of the Knight Family DIAN-TU sites all over the world – nearly 40 research institutes in North America, Australia, Europe, and South America to recruit individuals from families with DIAD. Trial participants will be 11 to 25 years before their expected age of dementia onset and have no or very few amyloid deposits in the brain.

Preventing or halting the earliest stages of disease could be transformative in the world of Alzheimer's prevention. Results will further our understanding of all forms of Alzheimer's disease, which could benefit the millions of people living with the more common late onset form of the disease. The trial is supported with funds from the National Institute on Aging (NIA), the Alzheimer's Association, GHR Foundation, Washington University, as well as St. Louis resident, Joanne Knight, a longtime benefactor of Washington University, and her family. The trial is being conducted in close partnership with Lilly, which also is providing significant funding.

This international effort to find ways to prevent Alzheimer's disease would not be possible without the support of many partners, as well as the active involvement of DIAD families. We thank our partners and the trial participants and their families for their ongoing commitment.

Pictured: Dr. Randall Bateman, director of DIAN and of the DIAN Trials Unit, offers a tour of his laboratory in the

newly opened Jeffrey T. Fort Neuroscience Research Building. (Photo by Matt Miller)



Alzheimer's Association International Conference (AAIC) 2024

On July 28-August 1, 2024, dementia science researchers, clinicians, and professionals will convene at the largest international conference on dementia research in Philadelphia, Pennsylvania, USA and

online. In addition to the formal scientific presentations and panels, the Alzheimer's Association will launch AAIC for All, which allows any member of the public to attend a specially curated track of highlights from AAIC either virtually or in-person for free. Additional information about accessing AAIC for All is available at <https://alz.org/aaic-for-all/overview.asp>.

Jamie Bartzel, the Expanded Registry Newsletter's editor, will also be attending AAIC in Philadelphia and sharing news and insights in the newsletter's next issue. If there are particular topics or sessions you want to see covered in this publication, email Jamie directly at bartzel@wustl.edu.

2024 DIAD Regional Family Conference

Just before AAIC begins, we will host the 2024 Regional Family Conference on Saturday, July 27, also in Philadelphia. This conference is open to families whose members carry DIAD genetic mutations and

living in the United States and Canada, as well as Alzheimer's researchers. This year's conference theme is *Moving Forward with Hope*.

The conference will be available via livestream for all DIAD families, with interpretation available in Spanish and French. If you are a member of a DIAD family or a professional in the field of Alzheimer's research and would like to learn more about attending the conference in person or accessing the livestream on our password-protected website, please email dianexr@wustl.edu for more information. We are excited to once again provide this opportunity for DIAD families to gather and share their experiences, support, and hope with one another.

DIAD Family Members: Share Your Story!

In a 2023 feedback survey, EXR Newsletter readers were invited to share their favorite (and least favorite) newsletter offerings. One request was unanimous:

family members and research professionals alike want to hear more personal stories!

We want to feature more individuals sharing what it's like to live with DIAD: whether as a person who knows their status, who is at risk of inheriting a genetic mutation, or as a caregiver or close loved one. What has been most challenging for you? Where have you found support? How has DIAD impacted your family dynamic? What do you wish healthcare professionals and researchers knew? What do you wish people would stop asking or assuming about you?

If you're interested in sharing your story, please contact me at bartzel@wustl.edu. All messages will be kept confidential! You can be as public or anonymous as you'd like; you can share identifying details or only state your relationship to this disease.

We hear from families, through the Expanded Registry and at Family Conferences, how meaningful it is for affected individuals to hear from people facing similar challenges. "I feel less alone" is a common sentiment. Others have stated that they felt empowered after sharing their story. If you think you might want to

share your experience, reach out to me—let’s have a conversation.

Jamie Bartzel

Resources for Caregivers

Jennifer Phillips, MPA, of Washington University’s Knight ADRC, offers an hourlong presentation on dealing with grief surrounding different types of dementia, with a particular focus on family members and caregivers of affected individuals. To access the video of this talk, as well as supporting resources, visit <https://knightadrc.wustl.edu/center-events/3rd-thursdays/>, and scroll down to “April 18, 2024: Grief and Loss in Dementia Caregiving.” You will be asked to complete a brief form to access the video.

A booklet from the Alzheimer Society of Canada, *Ambiguous Loss and Grief in Dementia: A resource for individuals and families*, offers guidance for the “type of loss you feel when a person with dementia is physically there, but may not be mentally or

emotionally present in the same way as before.” You can access this publication online at <https://alzheimer.ca/sites/default/files/documents/ambiguous-loss-and-grief-for-individuals-and-families.pdf>.

The journal *Narrative Inquiry in Bioethics* shares a free ebook, *Living with Alzheimer Disease and Other Types of Dementia: Stories from Caregivers*. This publication touches on a wide range of caregiving experiences across different types of dementia and can be accessed online at <https://d1a4a5.a2cdn1.secureserver.net/wp-content/uploads/2023/10/Alzheimer-FINAL-VOICES-publication.pdf>.

Recent DIAN Publications

“Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU): Trial Satisfaction and Attitudes towards Future Clinical Trials”

<https://doi.org/10.14283/jpad.2024.61>

“Downstream Biomarker Effects of Gantenerumab or Solanezumab in Dominantly Inherited Alzheimer Disease: The DIAN-TU-001 Randomized Clinical Trial”
<https://doi.org/10.1001/jamaneurol.2024.0991>

“Investigation of sex differences in mutation carriers of the Dominantly Inherited Alzheimer Network”
<https://doi.org/10.1002/alz.13460>

“Lessons learned from the failure of solanezumab as a prospective treatment strategy for Alzheimer’s disease”
<https://doi.org/10.1080/17460441.2024.2348142>

“Comparison of tau spread in people with Down syndrome versus autosomal-dominant Alzheimer's disease: a cross-sectional study”
[https://doi.org/10.1016/S1474-4422\(24\)00084-X](https://doi.org/10.1016/S1474-4422(24)00084-X)

“Examining amyloid reduction as a surrogate endpoint through latent class analysis using clinical trial data for dominantly inherited Alzheimer's disease”
<https://doi.org/10.1002/alz.13735>

The DIAN data are increasingly published in scientific reports to enable investigators worldwide to learn of our progress and to advance scientific understanding of Alzheimer's disease. Because of this, there is a small but possible risk that a DIAN participant reading or hearing of these scientific reports might guess, correctly or incorrectly, information about themselves. This includes guessing one's own or a family member's mutation status. We at DIAN take every step to minimize this risk, including ensuring that all DIAN data in journal articles, scientific meetings, press coverage, etc., lack identifying information for any participant, but it is possible that even such de-identified data may reveal a pattern of symptoms or a relationship with other medical disorders that could suggest that a particular person is mutation positive. You can avoid reading these scholarly articles or listening to presentations related to the DIAN study to decrease this risk.

Alzheimer's in the News

“How exercise increases brain volume – and may slow memory decline”

<https://www.washingtonpost.com/wellness/2024/01/24/exercise-brain-volume-memory/>

“Alzheimer’s blood test performs as well as FDA-approved spinal fluid tests”

<https://source.wustl.edu/2024/02/alzheimers-blood-test-performs-as-well-as-fda-approved-spinal-fluid-tests/>

“Neurons help flush waste out of brain during sleep”

<https://source.wustl.edu/2024/02/neurons-help-flush-waste-out-of-brain-during-sleep/>

“Immunotherapy for Alzheimer’s disease shows promise in mouse study”

<https://source.wustl.edu/2024/04/immunotherapy-for-alzheimers-disease-shows-promise-in-mouse-study/>

“Scientists Discover Possible New Treatment for Alzheimer's”

<https://www.newsweek.com/scientists-discover-new-treatment-alzheimers-1886548>

“Alzheimer’s disease progresses faster in people with Down syndrome”

<https://source.wustl.edu/2024/04/alzheimers-disease-progresses-faster-in-people-with-down-syndrome/>

“Alzheimer's drug adoption in US slowed by doctors' skepticism”

<https://www.reuters.com/business/healthcare-pharmaceuticals/alzheimers-drug-adoption-us-slowed-by-doctors-skepticism-2024-04-23/>

“Imaging technique shows new details of peptide structures”

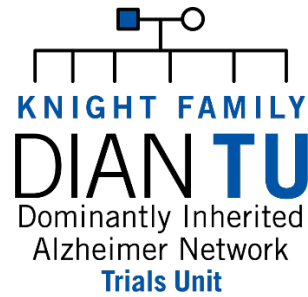
<https://source.wustl.edu/2024/04/imaging-technique-shows-new-details-of-peptide-structures/>

Scientific American special publication: “The New Age of Alzheimer’s”

https://sciam.bynder.com/m/28aa89a5b3ab388a/original/0524_Davos_SciAm_Final_Lo.pdf

“Moment of promise”

<https://source.wustl.edu/2024/04/moment-of-promise/>



Learn more about our research at <https://dian.wustl.edu>. If you are interested in research opportunities, contact the DIAN Expanded Registry at dianexr@wustl.edu. If you are not part of the registry and would like to be, visit <https://dian.wustl.edu/our-research/registry/> to register.

Contact the Editor

If you have an idea for a story or have questions about the information in this newsletter, please contact Jamie Bartzel: bartzel@wustl.edu

The DIAN Expanded Registry is supported by the Alzheimer's Association, GHR Foundation, an anonymous organization, private donors, the DIAN-TU Pharma Consortium, DIAN-TU industry partners, and the National Institute on Aging of the National Institutes of Health under Award Numbers U01AG042791, R01AG046179, R01/R56 AG053267, U01AG059798, and R01AG068319. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.