

DIAN-TU Treatment Trials

What's New with TU

Sunday, September 21, 2014

4:00 to 6:00 PM CDT

Presented by Randall Bateman MD

DIAN Trials Unit Director

DIAN Clinical Core Leader

Question and Answer Session

Agenda



- ❖ **Introductions**
- ❖ **Study updates**
 - **DIAN Obs**
 - **DIAN Expanded Registry**
 - **DIAN-TU Trial**
- ❖ **Discussion**

If you have a question during the webinar please go to the chat tab on the right hand side of your screen and type in your question or email it to: dianexr@wustl.edu

DIAN Update

The Dominantly Inherited Alzheimer's Network (DIAN) is an multi-center, international, observational, longitudinal study of individuals with or at risk for autosomal dominant AD.

- The DIAN has currently enrolled **400 participants**.
- DIAN funding has been renewed by the National Institute on Aging (UFI AG032438, JC Morris, PI) for an additional 5 years, with some planned changes.
 - 50 additional participants with focused enrollment criteria
 - Enrollment will target participants younger than parental age at onset, emphasizing those greater than 15 years younger than parental AAO.
 - Assessments every other year
 - Modified cognitive testing
 - The computerized cognitive battery has been amended to eliminate measures that were burdensome or duplicative of others
 - There are plans to add a CogState-based measures (to compare with those in the DIAN-TU assessments).

DIAN Research Aims for new funding cycle

1. Maintain the established international DIAN registry of individuals at risk for autosomal dominant AD (mutation carriers and non-carriers; presymptomatic and symptomatic) and assess participants every 2 years with the uniform DIAN protocol.
2. Recruit to the registry 50 new asymptomatic participants.
3. Maintain the integrated DIAN database and biospecimen repository to disseminate data and tissue to qualified investigators (within and outside of DIAN) in a user-friendly manner.
4. Utilize data obtained from DIAN research participants to support new scientific studies, including use of exome chip technology to examine potential modifiers of age at symptomatic onset.
5. Provide genetic counseling to any and all DIAN participants who wish to learn their mutation status and, for those who decide to learn their status after counseling, provide genetic testing by Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories (i.e., outside of DIAN).

** UFI AG032438, JC Morris, PI; the German Center for Neurodegenerative Diseases (DZNE) completely supports German DIAN sites.*

Additional support from an anonymous foundation & from the philanthropy of F Simmons and O Mohan

DIAN Obs Impact on DIAN-TU Therapeutic Trials

- **Trial development**: the participation of individuals and families in the DIAN Obs study has provided, and will continue to provide, crucial data used to design and develop DIAN-TU current and future trials.
- **Novel mutations**: continued participation in DIAN Obs is extremely important, especially in those cases where mutations found in families are not well known. Continued research on these mutations provides much-needed data as future trials commence.

DIAN Obs Procedure Completion Rates

(as of July 31, 2014)

| Procedure | Baseline N= 396 | Follow-up N= 290 |
|--------------------------------|----------------------------|-----------------------------|
| Cognitive battery | | |
| -Urinary Drug Screen (UDS) | 100% | 98% |
| -Computerized | 94% | 86% |
| Nonfasted Blood (for genetics) | 100% | N/A |
| Fasted blood | 97% | 98% |
| MRI | 94% | 90% |
| PET PIB | 87% | 83% |
| FDG PET | 90% | 88% |
| Lumbar Puncture | 80% | 69% |

Lumbar Puncture (LP)

- An LP allows cerebral spinal fluid (CSF) to be obtained for testing.
- CSF contains several key substances, called “biomarkers”, that are the focus of Alzheimer’s research, primarily A β 42 and Tau, two crucial proteins in the formation of damaging plaques and tangles.
- **Obtaining CSF via an LP is crucial to the success of the DIAN study, since there is no other way to obtain this important information.**

Imaging/Scans

- Imaging scans allow researchers to trace how A β circulates in blood serum and in CSF, to identify areas of A β deposition, and to track brain volume changes due to AD.
- The formation of A β plaques are one hallmark of Alzheimer's disease.

Psychometric Testing

- Memory and thinking tests are administered to ascertain actual cognitive functioning of participants.
- Some participants find these tests to be frustrating, but they are essential to better understand the progression of Alzheimer's disease.

Clinical Assessments

- Neurological and physical exams allow researchers to identify and track any changes that may be associated with Alzheimer's disease.

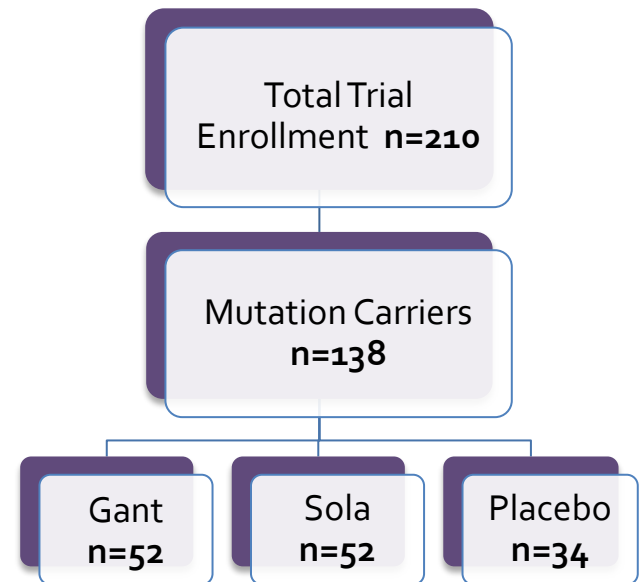
A complete picture...

Data obtained from all described components allow researchers to understand the pathology and progression of AD in order to develop better and more effective drugs.

When any of these study procedures are missed, the overall results of the research are undermined.

DIAN-TU Biomarker Trial Design

- Placebo controlled, double-blinded, biomarker outcome trial
- -15 to +10 years of parental age of onset; asymptomatic (>50%) to mild dementia (CDR 0.5-1)
- 3-arm trial:
 - 2 active drugs vs. 1 pooled placebo
 - Each active has a matching placebo
3:1 Active:Placebo
- 138 mutation carriers: 52 per active drug arm, 34 placebo
- Estimated 80 non-carriers (placebo)
- Drug treatment duration = 2 years



DIAN-TU-001 Trial Update

- Launched: Dec 2012
- First dose: March 2013
- Participants consented: 59
- Continued enrollment: next 6 -12 months
- Number of sites: 27
 - Australia (3)
 - Canada (3)
 - France (5)
 - Italy (2)
 - Spain (1)
 - UK (1)
 - USA/Puerto Rico (12)

DIAN-TU-001 Biomarker Trial Status

SITE STATUS

ACTIVE

1. US: Snider (Wash U, 12/12)
2. US: Roberson (UAB, 11/13)
3. US: Surti (Butler, 12/13)
4. US: Honig (Columbia, 12/13)
5. US: Van Dyck (Yale, 1/14)
6. US: Matthews (IU, 1/14)
7. US: Lah (Emory, 3/14)
8. AUS: Clarnette (Perth, 4/14)
9. AUS: Masters (Melbourne, 8/14)
10. UK: Mummery (UCL, 5/14)
11. FRN: Hannequin (Rouen, 5/14)
12. FRN: Formaglio (Lyon, 6/14)
13. FRN: Pasquier (Lille, 6/14)
14. FRN: Pariente (Toulouse, 7/14)
15. SPN: Sanchez-Valle (Barcelona, 8/14)
16. US/PR: Jimenez (UPR, 9/14)

PENDING

17. AUS: Brooks (Sydney)
18. CAN: Hsiung (UBC)
19. CAN: Gauthier (McGill)
20. CAN: Masellis (Sunnybrk)
21. FRN: Dubois (Paris)
22. ITL: Frisoni (Brescia)
23. ITL: Sorbi (Florence)
24. US: Ringman (UCLA)
25. US: Galasko (UCSD)
26. US: McDade (U Pitt)
27. US: Boxer (UCSF)

DIAN Trials Unit – Next Steps

- Continue **expansion of the DIAN-TU trial** to a cognitive endpoint drug registration trial *\$26.7M NIA grant (DIAN-TU APT) awarded in July 2014 (fully funded)*.
 - Seamless transition for most promising drugs
 - Interim analysis at one year to allow earlier transition
- Include **Tau imaging** as an add-on study to the DIAN-TU-001 trial *Funded by the Accelerating Medicines Partnership (AMP, FNIH/NIH)*.
- Re-design the trial to **test multiple drugs** in parallel. *Additional drug candidates are available in multiple stages, some potentially ready for trial entry in 2014.*
- **DIAN observational study site expansion** with additional international sites *Argentina, Italy, Spain, Japan, China, Korea, Canada.*

DIAN Expanded Registry (EXR)

Launched: February, 2012

Purpose: Provide participants with current and future research opportunities focused on autosomal dominant Alzheimer's disease. Currently, 2 studies are available (DIAN-TU Trial and DIAN Observational)

Process: After registering, the EXR Coordinator will contact you to collect more information about you and your family's experience with Alzheimer's disease. All collected information is stored on a secured server at Washington University, School of Medicine, in accordance with privacy protection protocols

Additional benefits:

- Source of information
- Media coverage about DIAN
- DIAN-TU Trial brochure and FAQ
- Archived webinars
- Exploratory Genetic Testing

DIAN EXR update

Total registrants: 712

- Individual & Family Registrants: 594
- Researchers & Professionals: 118

Number of individuals referred to Trial sites: 147

- 122 Registered participants & in DIAN Observational study
- 25 Registered participants

DIAN EXR: Exploratory testing

For families who have a strong history of early-onset Alzheimer's disease but have not had genetic testing:

- EXR can assist you in constructing a family history (pedigree)
- DIAN-TU team will review, and if approved, genetic counseling and testing will be provided to you free of charge
- EXR Coordinator identifies a genetic counselor in your area. If you decide to proceed with genetic testing, Coordinator will facilitate blood draw process.
- If an eligible mutation is found, you will be offered an opportunity to participate in DIAN research.

DIAN EXR

- **REGISTER** at www.dianexr.org
- Contact the DIAN EXR coordinator at dianexr@wustl.edu or by calling 1-844-DIAN-EXR (or +1-844-342-6397) to discuss questions related to your participation.
- More information on the DIAN-TU trial can be found at:
<http://clinicaltrials.gov/ct2/show/NCT01760005>

Be A Part of The Solution!

Dominantly Inherited Alzheimer's disease Drug Trials

- Does your family have one of the three known mutations that causes Alzheimer's Disease (AD)? - **OR** -
- Does your family have 3 generations of AD that starts younger than 60 years of age?

We are registering this specific group of people for drug trials. You might qualify if:

1. **You are over 18 years old and have a parent with Dominantly Inherited AD.**
2. **You are interested in participating in a drug study to test a drug that may slow down or prevent memory loss.**

The drug is provided free of charge and all expenses will be paid.

Risks will be discussed as part of the informed consent process.

**Register at www.dianexr.org
or 844-DIAN-EXR (342-6397)**



Participant Interaction & partnership: The Alzheimer's Association ADAD Forum

- Website launched February, 2011
- Currently, 51 members with 20 visits in the past 3 months, a decrease from earlier usage.



The ADAD Forum was designed to:

- facilitate the opportunity for participant and family members to connect on a secure web page for sharing personal blogs, asking for and giving support.
- The ADAD Forum has had input into the design of DIAN-TU clinical trials and trial design issues (e.g. placebo, genetic blinding, randomization).
- Ongoing webinars planned approximately twice yearly.

Ask your DIAN Coordinator how to join

Discussion Topics

- Duration of the current biomarker trial with transition to a cognitive endpoint trial (4 years or more total)
 - 2 years for the current biomarker stage
- Transition to Cognitive Endpoint trial
 - Impact on placebo-controlled group
 - Extension of treatment past 4 years
 - Long term possibilities (open-label extension)
- Status of the ADAD Forum

If you would like to ask a question or comment go to the chat tab at the right hand side of your screen or email your question to dianexr@wustl.edu.

The Dominantly Inherited Alzheimer's Network (DIAN) and the DIAN Trials Unit (DIAN-TU)

DIAN Principal Investigator

JC Morris

Coordinating Center Cores

Admin – JC Morris

Clinical – RJ Bateman

Biomarkers – AM Fagan

Biostatistics – C Xiong

DIAN-TU Principal Investigator

RJ Bateman

Genetics – AM Goate

Imaging – T Benzinger

Informatics – D Marcus

Neuropathology – NJ Cairns

Performance Sites

United States: Washington Univ, Univ Puerto Rico, Butler Hosp/Brown Univ, Columbia Univ, Indiana Univ, UCLA, UCSD, U of Pittsburgh, Mayo Clinic-Jacksonville, MGH/BWH, UAB, Yale, UCSF, Emory

Canada: UBC, McGill, Sunnybrook

Europe: Institute of Neurology-Univ College London, Ludwig-Maximilians-Universität München, University of Tübingen, Italy, France, Spain

Australia: Prince of Wales Medical Research Institutes-Sydney, Mental Health Research Institute-Melbourne, Edith Cowan Univ-Perth

THANK YOU!!!

QUESTIONS?

Participant perspective

If you have a question please go to the chat tab on the left hand side of your screen and type in your question or email it to: dianexr@wustl.edu

DIAN-TU Trial Information

Trial Inclusion/Exclusion Criteria

- Documented mutation on PSEN1, PSEN2, APP in the **family**
 - Participants do not need to know their own mutation status
 - If you know you are negative for the mutation, you are not eligible for the DIAN-TU trial.

**Participants enrolled in the Trial are eligible for genetic counseling and testing if they want to learn their mutation status*

Trial Inclusion/Exclusion Criteria

- 15 years before parental age of symptom onset to 10 years after parental age of onset
- Normal memory and thinking, very mild symptoms of memory loss, or mild dementia
- 18 years of age or older
- Family member or friend who accompany you to visits and provide information about your medical history

Trial Inclusion/Exclusion Criteria

- Devices for birth control (IUD, etc.) and other implanted medical devices (defibrillators, etc.) may not be compatible with the MRI scans.
- Visit this website on MRI scanning to check compatibility of implanted devices with a MRI.

http://www.radiologyinfo.org/en/safety/index.cfm?pg=sfty_mr

- Visit this website for details of PET scanning.

<http://www.radiologyinfo.org/en/info.cfm?pg=pet>

Placebo

- Placebo contains no active medication but looks like and is administered the same as the active drug.
- FDA standard for clinical trials (normally 50%)
- In this trial, **75% of mutation carriers** will receive active drug and 25% will receive placebo
- All mutation-negative participants will receive placebo.
- Intravenous or subcutaneous injection of placebo.

Study Drugs

Solanezumab & Gantenerumab

- Monoclonal antibodies that bind to beta-amyloid.
- Passive immunization.
- Modify early changes in the brain caused by beta- amyloid.

Drug Delivery/Side Effects

Solanezumab

- Given by intravenous infusion for 30 minutes
- Participant observed for 2 hours afterwards to watch for side effects.
- Trial monitors for side effects and maintains dosing of the drug and safety visits.

Drug Delivery/Side Effects

Gantenerumab

- Given subcutaneously, just under the skin on the belly
- Trial monitors for side effects and maintains dosing of the drug and safety visits.

Study Visits

- Screening Visit: home or at Trial site
- Initial Baseline Visit, additional screening and Complete Assessment: Trial site
- Drug administration and check-up: monthly at your home or where convenient for you
- Safety MRI: every 3 months, near where you live
- Annual Visit: Trial site for all tests

Screening visit

- Assess preliminary eligibility and conduct safety testing before Baseline Visit at DIAN-TU trial site
- Collection of demographic information, vital signs, medical/surgical history, genetic testing, safety labs (including pregnancy testing) and memory and thinking practice testing
- May take place at the DIAN-TU trial site, your home or other location or site as requested
- The Screening visit usually takes 3 to 4 hours, and is arranged at your convenience, including weekends and evenings

Baseline Visit

Additional screening

- **Screening EKG**
 - to look for any cardiac (heart) abnormalities.
- **Safety MRI**
 - which looks at the structure of the brain.

Baseline Assessments

If eligible, the following biomarker studies will be completed:

- **Three PET scans**
 - scheduled over the entire visit. Each PET scan uses a small amount of a radioactive tracer to observe either the energy use of the brain or the presence of amyloid plaques.
- **Lumbar puncture**
 - for collection of cerebrospinal fluid.

Baseline Visit cont'd

- **A clinical evaluation with a study clinician**
 - to assess for changes in memory and thinking, judgment, personality and mood. The clinical exam will include a physical and neurologic exam.
- **Paper-pencil and computerized testing**
 - to assess your memory and thinking abilities.
- **Blood sampling**
 - to determine if there are certain markers in the blood (and if so how much) that might indicate the presence of disease.

Baseline Visit cont'd

- **Blood sampling for genetic testing.**
 - Your blood will be sent to a study approved lab using a unique ID number to test for the reported family mutation. You will not receive the results of this testing. If, during your study participation, you wish to learn your mutation status, the study team will refer you to a certified genetic counselor.
- Baseline Visits last 4 days and takes place at your trial site

DIAN Observational Participants

- **If I am already in the DIAN Observational study, can I transition to the trial?**

Yes, the DIAN-TU is coordinating with Obs study sites to ensure that you are offered an opportunity to join the trial if you meet certain additional eligibility criteria. Great efforts are being made to make the transition as smooth as possible.

Considerations include:

- *Last In-clinic DIAN Observational study visit*
 - *Coordinate transition timing to account for any local requirements/regulations for radiation limits*
 - *Coordinate to ensure DIAN visits and data are not compromised*
 - *Site capacity (sites have a participant cap per month)*
 - **If so, do I participate at my DIAN Site?**
- Yes, but you may also decide to enroll at a trial site closer to your home.*
- **If I am found ineligible for the trial, will I be offered the chance to participate in the DIAN Observational study?**

Yes, if you can't participate in the trial, you can resume participation in the Observational study. If you are new to DIAN research and you meet eligibility criteria for the Observational study, you will be referred to an Observational study site coordinator to make arrangements.

Trial duration, etc.

- **How long is the trial?**

The first part of the trial is two years. Depending on the success of the drugs, it may last longer.

- **Who administers the monthly treatments?**

Home health care visiting nurses contracted by DIAN-TU

- **Are weekend treatments available?**

Yes, weekend and evening treatments are possible.

- **Can participants taking medications for memory impairment (Namenda[®], Aricept[®], Razadyne[®], Exelon[®]) remain on their medications during trial participation?**

Yes, but we ask that the dose stays the same. You would discuss this with the study nurse.

Active drug vs. placebo

- **Who decides whether participants get the active drug or placebo?**

A computer system randomly assigns participants to active drug or placebo. The assignment to drug or placebo is “blinded”, which means neither the participant nor any member of the study team will know whether the individual is receiving the study medication or placebo. All mutation negative participants will be assigned to placebo for safety purposes, and so that mutation status is not revealed to the participant or the study team.

Side effects

- **If you have side effects from a drug, does that mean that you are mutation positive?**

No. Even people on placebo may have side effects. A side effect is likely to be mild and may not be different from everyday type discomforts such as headache, fatigue, and nausea. All side effects that you experience will be documented.

The trial will evaluate the biomarkers for changes to determine if there is a response to the study medication.

Genetic Counseling & Testing Process

- **Can I get genetic testing once I'm enrolled in the trial?**
Enrolled trial study participants who indicate they wish to know their mutation status will be referred to a genetic counselor. The cost of the genetic counseling and testing will be paid for by the study. This service is provided by the study, and is optional.
- **How does finding out my status affect my participation?**
If you choose to have the genetic testing performed and the results indicate you are a carrier of an autosomal dominant mutation, we ask that you do not share these results with the study team. If you are found not to carry a mutation, you will no longer be eligible to participate in the trial