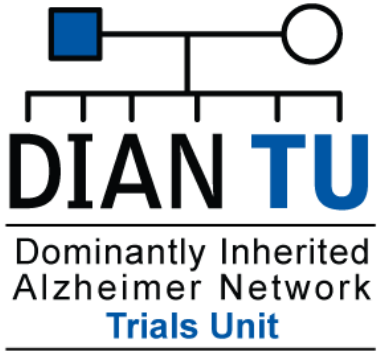


# DIAN-TU Treatment Trials
# What's New with TU
# Sunday, April 13, 2014

**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
- DIAN-TU Trial & DIAN Observational study updates
- Frequently-asked questions:

  DIAN-TU Trial
- Questions & answer session

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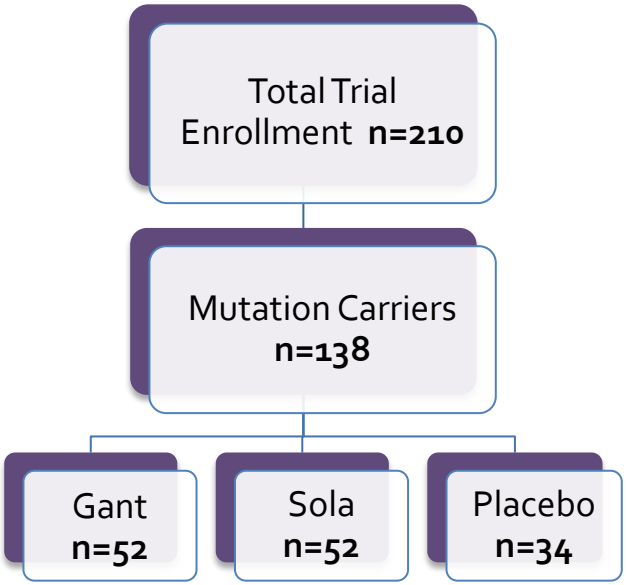
# DIAN-TU Biomarker Trial Design

- 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

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# DIAN-TU-001 Trial Update

- Launched: Dec 2012
- First dose: March 2013
- Participant enrollment: 24
- Number of sites:
  - North America (US/CAN/PR): 15*
  - International: 12

**Participants in Puerto Rico complete annual visits at Columbia U*

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# DIAN-TU Trial Sites (North America)

**The following sites are currently enrolling for the DIAN-TU trial:**

**USA**

1) Washington University in St. Louis (MO)
2) University of Alabama at Birmingham (AL)
3) Yale University (New Haven, CT)
4) Emory University (Atlanta, GA)
5) Columbia University (NY)
6) Indiana University (Indianapolis, IN)
7) Butler Hospital/Brown University (Providence, RI)

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# DIAN-TU Trial Sites (North America)

**The following sites will be enrolling by late Spring/early Summer 2014:**

**USA**

8) University of Pittsburgh (PA)
9) University of California-Los Angeles (CA)
10) University of California-San Diego (CA)
11) University of California-San Francisco (CA)

**CANADA**

1) University of British Columbia Hospital (Vancouver, BC)
2) McGill University (Montreal, QC)
3) Sunnybrook Health Sciences Centre (Toronto, ON)

**PUERTO RICO**– University of Puerto Rico (via Columbia Univ)

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# DIAN-TU Trial Sites (International)

**The following sites will be enrolling by late Spring/early Summer 2014**

**AUSTRALIA**

1) Neuroscience Research Australia (Sydney)
2) The McCusker Alzheimer's Research Foundation (Perth)
3) Mental Health Research Institute (Melbourne)

**FRANCE**

1) Groupe Hospitalier Pitie-Salpetriere (Paris)
2) Hopital Neurologique Pierre Wertheimer (Lyon)
3) CHU de Lille—Hopital Roger Salengro
4) CHU de Toulouse—Hopital Purpan
5) CHU de Rouen—Hopital Charles Nicolle

**ITALY**

1) Centro Regionale di Neurogentica
2) IRCCS Centro San Giovani di Dio Fatebenefratelli

**UK** – University College at London

**SPAIN** -- Hospital Clinic i Provincial de Barcelona

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# Dominantly Inherited Alzheimer Network (DIAN)* Research Aims

1. Establish an **international registry** of participants at risk for autosomal dominant AD (mutation carriers and non-carriers; presymptomatic and symptomatic).
2. Evaluate clinical and cognitive measures with imaging, CSF, and blood biomarkers in a uniform manner at entry and **longitudinally** thereafter.
3. Determine the temporal **order** and **rate of change** of AD changes in clinical, cognitive, neuroimaging, and biomarker indicators.
4. **Compare** the clinical, cognitive, imaging and biomarker indicators, and neuropathology of autosomal dominant AD to those **of late-onset "sporadic" AD**.
5. **Design and perform DIAN with future treatment trials, per NIH request.**

*The DIAN has currently enrolled **371 participants** and expects to reach **400** by May, 2014.*

***U19 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***

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

**DIAN Principal Investigator**
**JC Morris**

**DIAN-TU Principal Investigator**
**RJ Bateman**

Coordinating Center Cores

Admin – JC Morris
Clinical – RJ Bateman
Biomarkers – AM Fagan
Biostatistics – C Xiong

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**

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# 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

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# DIAN EXR update

Total registrants: 625

- Individual & Family Registrants: 525
- Researchers & Professionals: 100

Number of individuals referred to Trial sites: 106

- 98 Registered participants & in DIAN Observational study
- 8 Registered participants

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# DIAN EXR: Exploratory testing

For families who have a strong history of early-onset Alzheimer's disease but have never 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.

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# DIAN EXR

- **REGISTER** at www.dianexr.org
- Contact the DIAN EXR coordinator at dianexr@wustl.edu or by calling 1-844-DIAN-EXR (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

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# 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)

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


- Website launched February, 2011
- Currently 51 members, 682 user logins, 6405 page views and 60 posts.

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**

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# Next Steps

- DIAN site expansion with additional international sites
- Trial Design Modifications
  - Design trial to allow for continuous addition of drugs
    - Additional drug candidates are available in multiple stages
  - Seamless transition to Phase 3 registration trial for most promising drugs
    - Cognitive/Clinical outcome
    - 4 year duration

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# Slowing of Cognitive Decline

What kind of benefit does the drug need to have to be worthwhile based on the risks? What is meaningful for slowing of cognitive decline?

- Delay/prevention of disease:
  - 6 months? 1 year? 2 years? 5 years? 10 years?
  - Life-long prevention
- Risks:
  - Side-effects (none, mild, severe)
  - Administration (burdensome or not)
  - Cost to patient

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# Discussion

# Frequently-Asked Questions

# 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*

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# 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

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# 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.

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# Study Drugs

## Solanezumab & Gantenerumab

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

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# 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.

Rare side effects:

  - Increased water content of brain tissue
  - Small bleeds in the brain tissue (micro-hemorrhage).

Side effects are monitored by brain MRIs every 3 months.

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# 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.

Rare side effects:

  - Increased water content of brain tissue
  - Small bleeds in the brain tissue (micro-hemorrhage).

Side effects are monitored by brain MRIs every 3 months.

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# 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

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# 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

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# 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.

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# 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.

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# 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

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# 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 coordinator to make arrangements.*

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# 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®, Excelon®) 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.*

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# 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.*

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# 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.*

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# 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.*

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# THANK YOU!!!

QUESTIONS?

Participant perspective