DIAD Family Webinar
Saturday, December 9, 2017
3:00-5:00 PM CST / 9:00-11:00 PM GMT

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Agenda

• Re-Cap of 2017 DIAD Family Conference
• DIAN-TU Third drug arm
• Primary Prevention update
• DIAN Observational study renewal
• Questions and Answers

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
2017 DIAD Family Conference

Key to the Cure

Saturday, July 15th

University College London, ICH • London, England

Total attendees: 280
- 152 family members from England, Ireland, Scotland, Wales, France, Italy, Spain, Germany, Sweden, The Netherlands, Canada, United States, Colombia, Argentina, Australia, Japan and China
- 128 researchers/professionals

2018 conference is July 21st in Chicago, IL USA
**DIAN Therapeutic Trials Rationale**

- Clinical **onset of symptoms can be predicted at any point** in lifespan, allowing therapeutic trials years or even decades before the clinical onset.
- **DIAD has a clear cause of disease due to amyloid-beta: ‘pure AD’ without interference from other diseases**
- **Uniquely informative scientific information of disease progression, biomarkers and changes due to therapeutic treatments**
- **Common pathophysiology support general AD indication**
- **Successful implementation of prevention and symptomatic studies will inform as to the cause of AD and provide guidance for future therapeutic development.**
DIAN-TU Aims

- Execute **pioneering prevention studies** in DIAD utilizing observational data from DIAN, disease progression models, comprehensive biomarkers, input from participants and family members, and inclusive discussions with stakeholders.
  - “It is really cutting edge, and it is the right thing to do – the trial, the observational study......” Janet Woodcock, 2015 DIAD Family Conference, [https://dian-tu.wustl.edu/en/2015-family-conference/](https://dian-tu.wustl.edu/en/2015-family-conference/)
- Identification and **registration of effective therapeutics** for DIAD patient use
- Determine the **timing of AD treatment** important for improved clinical outcomes
- Identify **changes in physiologic or pathologic biomarkers** that can be used to track therapeutic effectiveness of AD treatments and develop **surrogate biomarkers**.
- **Test AD hypotheses** (e.g. amyloid hypothesis) through therapeutic treatment trials
Through public/private support and partnership, the DIAN-TU has launched trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer’s disease drug developments.

*Financial support has also been provided by anonymous sources.
**DIAN-TU Trial Design**

Enrollment of both mutation carriers and non-carriers. Option of non-disclosure of genetic status to participate in the DIAN-TU trial.
DIAN-TU Trial Updates

• Importance of up-titration of solanezumab
  – Rationale
    • Biomarkers suggest dose can be increased
    • New data indicates clear evidence of dose-dependent biological activity for aggregated amyloid beta-targeting monoclonal antibodies, and higher doses are more likely to provide a higher pharmacodynamic effect.
    • Recent Amyloid PET results from Gantenerumab AD studies (NOT DIAN-TU) support the increased dose implemented in DIAN-TU

• Importance of staying in the study
  – Provides longitudinal information (changes over time)
  – Most important information about treatment comes in last 2 years of trial

• Challenges
  – Participant burden
  – Long prevention trial
DIAN-TU NexGen Trial Design

DIAN-TU NexGen:
- New drug arms
- 4 years of treatment
- Novel biomarkers
- Uses DIAD-specific Disease Progression Model based on DIAN Obs. data.
- Cognitive interim analysis
- Dose adjustment for maximal effect
- Home-based cognitive testing
- Population: with or at-risk for a DIAD mutation; -15 to +10 years of EYO; CDR 0, 0.5, 1.
NexGen Trial is underway!

• 7 sites now open in the United States
  – Washington University (St. Louis, MO)
  – Indiana University (Indianapolis, IN)
  – University of Alabama (Birmingham, AL)
  – University of California (San Diego, CA)
  – Yale University (New Haven, CT)
  – Emory University (Atlanta, GA)
  – University of Pittsburgh (Pittsburgh, PA)

• 1 in Canada (McGill University, Toronto)

• 1 in Spain (Hospital Clinic, Barcelona)

DIAN Expanded Registry coordinators are contacting family members who have expressed interest in joining the trial to facilitate referrals to open sites. Please send an email to dianexr@wustl.edu if you are interested in a referral to the DIAN-TU trial.
A brief history of Alzheimer’s disease modifying prevention

1906 - Dr. Alois Alzheimer describes first Alzheimer’s disease patient – disease of brain – plaques and tangles

1906 - Mutations discovered that cause early onset Alzheimer’s in families – later discovered in Alzheimer’s first patient

2000’s – first drugs targeting Aβ - A cause of Alzheimer’s are developed

2012 - Aβ lowering mutation discovered which dramatically protects against Alzheimer’s

2012 – first prevention trial against amyloid-beta is launched

2014 - Prevention trials targeting at-risk individuals

2017 - Prevention trials with oral secretase inhibitors

2018? - Primary Prevention
What’s next

DIAN-TU PRIMARY PREVENTION AND DIAN OBSERVATIONAL STUDY RENEWAL
Estimated slowing of disease by point of intervention and effect size of intervention

30% secondary prevention cognitive decline
5 years delay to symptomatic

Proportional/Time Slowing Treatment Effect Treated at EYO -15

%Change in Decline (Solid)
%Slowing Time (Dash)

CDR 0.5
CDR 1-2
Timing of AD prevention trials related to core pathology and symptom onset

- **Primary Prevention trials**
  - -25 years
  - Amyloid plaques

- **Secondary Prevention trials**
  - -15 years
  - Tau tangles

- **Symptomatic trials**
  - Mild dementia
  - Cognition

20-30 year process from pathology onset to time of death
Primary Prevention

- Grant submitted Oct 2017
- Population:
  - With or at-risk for a DIAD mutation (does not require you to know your genetic status)
  - 18 years of age and older
  - More than 15 years before estimated symptom onset
  - Cognitively normal (CDR = 0)
Considerations for Primary prevention

– Duration (multiple phases of the study- up to 10-15 years total)
– Low likelihood of symptoms (placebo considerations and side effects considerations)
– Family planning
– Type of therapy
DIAN Obs Productivity

- 104 publications
- 16 presentations at 2017 Alzheimer’s Association International Conference in London, England UK
- 43 sets of samples shared with investigators, domestic & global
- 125 data sets shared with investigators, domestic & global
- Data used to design and implement 3 arms in the DIAN-TU trial
DIAN Observational Study Renewal

1) Planned submission in 2018 for funding 2019-2024, with increased recruitment
2) Focus on molecular cause of Alzheimer’s
3) Tau PET imaging
4) Harmonization of DIAN-TU and DIAN EXR
Participant Interaction and Partnership
DIAN Expanded Registry

Serves as a key information and referral source for the DIAN Observational and DIAN-TU trials

Register: www.dianexr.org
Call: 1-844-DIAN-EXR (342-6397)
Email: dianexr@wustl.edu
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 Administrative and Clinical Operations Team

Randall Bateman – Director and PI, Eric McDade – Associate Director

DIAN-TU Cores

Administrative: Randall Bateman and team
Biomarkers: Anne Fagan and team
Biostatistics: Chengjie Xiong, Guoqiao Wang and team
Cognition: Jason Hassenstab and team
Genetics: Alison Goate, Carlos Cruchaga and team
Imaging: Tammie Benzinger and team
Neuropathology: Nigel Caims and team

We gratefully acknowledge the DIAN and DIAN-TU participants and family members, DIAN Team, DIAN Steering Committee, Knight ADRC, Alzheimer’s Association, ADAD Forum, NIH U01AG042791, R01AG046179, R01AG053267, R13AG055232, DIAN-TU Pharma Consortium, GHR, Anonymous Foundation, Industry Partners (Eli Lilly, Hoffman-LaRoche, Janssen, Avid Radiopharmaceuticals, Bracket, Cogstate), and Regulatory Representatives.

DIAN-TU Collaborators

Project Arm Leaders: Steve Salloway, Martin Farlow, Lon Schneider
Consultants: Berry Consultants, Cornelia Kamp, Cardinal Health Regulatory Sciences, Granzer Regulatory Consulting

DIAN-TU Therapy Evaluation Committee: Paul Aisen, Randall Bateman, Dave Clifford, David Cribbs, Bart De Strooper, Kelly Dineen, David Holtzman, Mathias Jucker, Jeffrey Kelly, Virginia Lee, Cynthia Lemere, Eric McDade, Susan Mills, John Morris, James Myles, Laurie Ryan, Matthias Staufenbiel, Raymond Tait, Robert Vassar

DSMB Members: Gary Cutter, Steve Greenberg, Scott Kim, David Knopman, Willis Maddrey, Kristine Yaffe
ADCS: Ron Thomas
ATRI: Paul Aisen

University of Michigan: Robert Koeppke

Mayo Clinic: Clifford Jack
DIAN-TU Trial Performance Sites

**Australia**
Neuroscience Research Australia, William Brooks
The McCusker Foundation, Roger Clarnette
Mental Health Research Institute, Colin Masters

**Canada**
McGill University, Serge Gauthier
UBC Hospital, Robin Hsiung
Sunnybrook Health Sci Centre, Mario Masellis

**France**
Hopital Roger Salengro, Florence Pasquier
Hopital Neurologique Pierre Wertheimer, Maité Formaglio
CHU de Rouen, Didier Hannequin
CHU de Toulouse, Jérémie Pariente
Groupe Hospitalier Pitie, Bruno Dubois

**Italy**
IRCCS Centro San Giovanni di Dio Fatebenefratelli, Giovanni Frisoni
Azienda Ospedaliera Universitaria Careggi, Sandro Sorbi

**Spain**
Hospital Clinic I Provincial de Barcelona, Raquel Sanchez Valle

**United Kingdom**
The National Hospital for Neurology & Neurosurgery, Catherine Mummery

**United States**
Columbia University, Lawrence Honig
University of Puerto Rico, Ivonne Jimenez-Velazques
Indiana University, Jared Brosch
University of Pittsburgh, Sarah Berman
Washington University, Joy Snider
University of Alabama, Erik Roberson
Butler Hospital, Ghulam Surti
Emory University, James Lah
Yale University, Christopher Van Dyck
University of California, San Diego, Doug Galasko
University of Washington, Seattle, Suman Jayadev

**Potential future DIAN-TU countries/sites:** Argentina, Brazil, China, Colombia, Germany, Hong Kong, Ireland, Japan, Korea, Mexico, Netherlands; New US site locations include Chicago, Dallas and Los Angeles