

**DIAN TU WEBINAR**

**Date: Sunday, February 10, 2013**

**Time: 4:00 PM to 6 PM**

**1. The DIAN Treatment Trials.**

**Slide 1.**

The DIAN Treatment Trials:  
An Update

Sunday, February 10, 2013  
4:00 to 6:00 PM CDT

Presented by Randall Bateman M.D.  
DIAN Therapeutic Trials Unit Director  
DIAN Clinical Core Leader

**2. Agenda, Introductions and Questions from Participants.**

**Slide 2.**

Agenda  
Introductions  
Questions and Answers  
From DIAN participants  
On  
DIAN Therapeutic Trials Units

**3. Review of Inclusion/Exclusion Criteria.**

**Slide 3.**

***Inclusion/Exclusion***

- 15 years before parental age of onset to 10 years after parental age of onset
  - Participants include individuals without impairment but includes
    - People with possible symptomatic, or mild dementia
    - Greater than 18 years of age

**4. Will an individual's stage of disease (mildly vs. greatly symptomatic) affect their eligibility?**

The inclusion criteria allows for someone to be cognitively normal (no memory or thinking problems) or mildly symptomatic. Mildly symptomatic includes people with very mild memory and thinking problems including mild dementia, but does not include people with very severe memory and thinking problems.

**5. Do Participants need to know their own mutation status?**

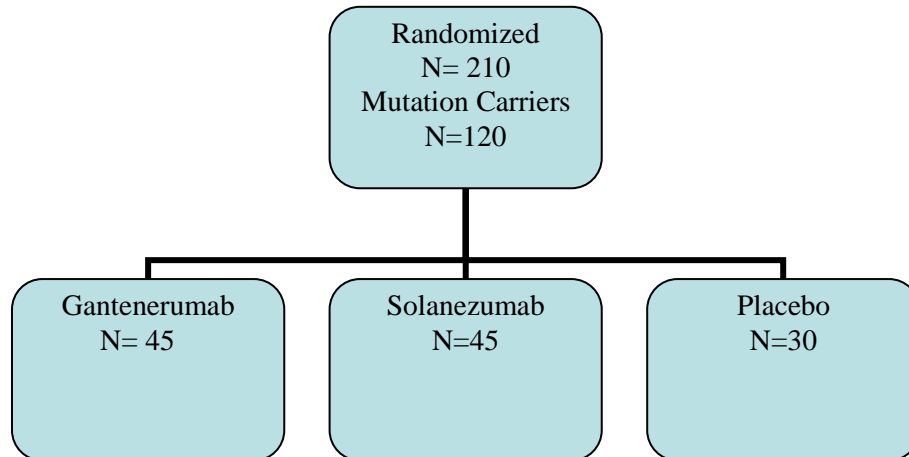
No, participants are not required to know their mutation status in order to participate in the trial. However, if a person knows his/her mutation status is negative, they will not be permitted to enroll in the trial. He/she is no longer considered "at risk" of carrying the family mutation and does not meet study inclusion criteria. As part of the study, blood will be collected for genetic testing but the results are for research purposes only. You and members of the study team will not receive any results. Participants identified as mutation negative through the blinded genetic research testing will be assigned to placebo. Again, you and members of the study team will not be informed of the results from the genetic research testing or assignment to study drug or placebo.

**6. What is a placebo and does the trial have to have one?**

The test drug is compared with an inactive preparation designed to resemble the test drug. A placebo-controlled study may include additional treatment groups, such as an active treatment group or more than one dose of the test drug, and usually includes randomization and blinding of patients or investigators, usually both. This is a requirement of the FDA and is very important in order to prove that a drug is effective.

**7. How is it decided which trial drug the participant is to receive?**

This study will have 3 arms (Gantenerumab, Solanezumab and placebo). Mutation positive participants will be "randomized" to one of the 3 study arms. This means that they will be assigned by chance to one of the treatment arms. Participants in the treatment arm have a 75% chance of receiving active drug. Put another way, there is a ratio of 3:1 drug:placebo. Most research trials have only a 50% chance of receiving drug. Participants who are mutation negative will be assigned to the placebo group. Mutation negative participants are included to maintain blinding as to genetic status for those who do not wish to know their genetic status. Mutation negative participants are not included in the efficacy analyses as they will not be exposed to study drug.

**Slide 4****8. Can you describe the drugs in more detail?**

This study is sponsored by Washington University in collaboration with Eli Lilly (“Lilly”) and Hoffman-LA Roche (“Roche”), makers of the drugs included in this clinical trial, and the Alzheimer’s Association. The goal of the study is to determine the safety, tolerability, and potential response of two potentially disease-modifying therapies in individuals at risk of having a gene mutation that causes dominantly inherited Alzheimer’s disease.

The two initial drugs are Solanezumab (Lilly) or Gantenerumab (Roche). Both study drugs are monoclonal antibodies that bind to beta amyloid. Beta amyloid is a protein that accumulates in the brain of people with Alzheimer’s disease. The abnormal accumulation of beta amyloid protein in the brain is thought to play an important role in the symptoms of memory loss and confusion. It is hoped that one or both of the study drugs will attach to the beta amyloid protein and help the body to remove it from the brain.

Both therapies used in this clinical trial, Solanezumab and Gantenerumab, act as a form of “passive immunization” in the body. When someone is immunized, special proteins called antibodies become active in the body. Antibodies help in a body’s defense against infection or disease. “Passive immunization” occurs when antibodies are given directly so the body does not need to make its own. The drugs used in this study are antibodies and this treatment is a type of “passive immunization.” The purpose of this study is to determine if each study drug (independently) can modify the early changes in the brain caused by amyloid beta, the protein that forms the amyloid plaques thought to play a role in Alzheimer’s disease.

## 9. Do you know what the possible side effects are?

Yes, for the purposes of saving time, I would like to summarize what those side effects are, and highlight the most significant effects. When you are considering the study you will have ample time to review the side effects, and ask any and all questions you have about them.

First, I would like to review the side effects for Solanezumab. The list of side effects will be listed in the consent, with the full explanation of side effects. It is important to know that many people have been on Solanezumab, and anything the participant experiences during this time is documented. The relationship of the event to the drug is considered, thoroughly and carefully.

Solanezumab will be administered by intravenous (IV) infusion. The procedure IV infusion will take about 30 minutes. You will need to be observed for 2 hours after the IV infusion of study drug after the first two infusions to be sure you do not have any reactions or bad effects.

Participants are followed closely, and any sign of illness is documented, and followed until it is resolved.

Two types of changes have been reported in people who have had passive immunization treatments (not just in Solanezumab and Gantenerumab but also in other large trials of other antibodies. We do not yet know how frequent these changes will be with Solanezumab and Gantenerumab).

Increased Water Content of the Brain Tissue (vasogenic edema): An increase in the water content of the brain tissue has been seen in some people taking experimental agents that lower a brain protein thought to cause Alzheimer's Disease. Symptoms that can happen if someone has an increase in water content in the brain include headache, worsened confusion, change in level of consciousness, seizures, unsteadiness/dizziness and vomiting, but there may not be any symptoms with this kind of increase in water content in the brain.

Increase in Small Bleeds in the Brain Tissue (micro-hemorrhage): An increase in the size or number of small bleeds in the brain tissue has been seen in about 9% of people taking Solanezumab compared to 7% of people taking a substance that looks like Solanezumab but has no medicine in it (placebo). There was no difference in the seriousness (symptoms) of small bleeds in Solanezumab-treated patients compared to placebo treated patients.

Brain MRI scans will be performed to monitor for any development of abnormal water content or these small bleeds in the brain. Should these occur; the treatment program will be adjusted or stopped as medically indicated.

The second drug is Gantenerumab. Again, many people have been administered Gantenerumab. Many of the side effects such as headache or rash are something that happens to people on an occasional basis. The drug study will keep track of any possible side effect you may be having and monitor you frequently which means the study nurse will be in contact with you until the side effect is resolved. Gantenerumab will be administered by subcutaneous injection which is under the skin. The most likely side effects are pain or reactions where the injection is given. This happened to less than 15% of the people in the study.

Increased Water Content of the Brain Tissue (vasogenic edema): An increase in the water content of the brain tissue has been seen in some people taking experimental agents that lower a brain protein thought to cause Alzheimer's disease. Symptoms that can happen if someone has an increase in water content in the brain include headache, worsened confusion, change in level of consciousness, seizures, unsteadiness and vomiting, but there may not be any symptoms with this kind of increase in water content in the brain.

Increase in Small Bleeds in the Brain Tissue (micro-hemorrhage): An increase in the size or number of small bleeds in the brain tissue has been seen in 10 people who have been in studies of gantenerumab. In 6 of these people, the brain MRI also showed areas with increased water content. None of these people had any symptoms associated with the small bleeds. Only 2 people stopped participating in the study as a result of these changes.

Brain MRI scans will be performed at regular intervals during the DIAN-TU-001 study to monitor for any development of abnormal water content or these small bleeds in the brain. Should these occur; the treatment program will be adjusted or stopped as medically indicated.

## **10. How will the study be administered? Slide 5.**

You will remain in the study for 24 months. You will complete study safety and infusion or injection visits every four weeks (approximately). A member of a study team will assist with scheduling of all study visits. You will be asked to complete safety MRIs approximately every three months. A schedule of study visits is included in the study consent.

Once all screening procedures are completed and eligibility for participation has been confirmed, you will be randomized to a treatment arm of the study – either Solanezumab versus placebo or Gantenerumab versus placebo. You and members of the study team will not know whether you are on study medication or placebo. You will not be able to choose the study treatment arm. If you have the mutation that causes Alzheimer's Disease in your family, you will have a 3 out of 4 chance of

receiving study medication and a 1 out of 4 chance of assignment to placebo. If you do not have the mutation that causes Alzheimer's Disease in your family you will automatically be assigned to the placebo group. Once you are randomly assigned to a study treatment arm, a member of the study team will review the study drug specific consent. You will receive the first dose of study medication on Day 3 of the baseline visit. All baseline study procedures (e.g. LP, blood for biomarkers, MRI, and PET) will be completed again at 1 year and at 2 years after you start the study.

## Slide 5: Study Schedule

### 11. How frequent are the study visits?

You will be asked to complete a Screening Visit (V01), Baseline Visit (V02), monthly study visit for drug administration and safety checks, , safety MRIs once every three months (approximate), and yearly visits at the DIAN center lasting three to four days. The screening visit and monthly study visits may take place in your home or at the DIAN center. Safety MRIs may be completed at the DIAN center or an approved imaging center near where you live.

## Slide 5

Visit Type	Screen	Baseline, Yr 1 & Yr 2	Every 6 Mo.	Every 3 Mo.	Every Mo.
<b>Timing (weeks)</b>	<b>-2 to -8 Wks</b>	<b>Wk 0, 52, 104</b>	<b>Wk 24 &amp; 76</b>	<b>...</b>	<b>...</b>
Your study doctor will check that you are suitable to take part in the study	X	X			
Your study doctor or nurse will ask questions about other medicines you are taking, about your Alzheimer's disease and your medical history	X	X			X
Your study doctor will perform a physical and/or neurological examination		X			
An ECG (recording of your heart activity) will be performed		X	X		
Your blood pressure, pulse rate, body temperature & breathing will be measured		X	X	X	
Blood and/or urine samples will be collected	X	X	X		
Pregnancy Test	X				X
You will receive Study Drug on these days		X			X
You will stay on site for 2 hours after infusion/injections		X			
A MRI brain scan will be performed		X		X	
Lumbar Puncture, MRI, & PET Scans will be done		X			
Memory and Thinking Assessments will be done		X	X		
Study staff will ask you how you are feeling, and about any other medicines that you are taking	X	X			X
Study staff will ask you about your mood and risk for suicide	X	X		X	

## 12. What is the Baseline Visit? Slide 6

At the baseline visit, the screening process will determine eligibility, and biomarker studies completed. Specifically, you will be asked to complete:

- A screening EKG to look for any cardiac (heart) abnormalities.
- An MRI which looks at the structure of the brain.
- 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.
- A lumbar puncture for collection of cerebrospinal fluid.
- A clinical evaluation with a study clinician to assess for changes in memory and thinking, judgment, personality and mood. A study physician will also complete 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.
- 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.

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IRB ID #: 201111194  
 APPROVAL DATE: 05/24/16  
 RELEASED DATE: 05/27/16  
 EXPIRATION DATE: 05/23/17

Day 1	Day 2	Day 3	Day 4
		<b>7:00</b> CSF and fasting blood collection 2.5 hours	Early AM departure home.
<b>07:30</b> Informed consent discussion 1 ~ 1.5 hours Urine pregnancy test if indicated	<b>08:00</b> Psychometrics 2.5 hours	*Late Breakfast by 8:00 (To begin fasting after breakfast.)	
09:00 MRI 2 hours	<b>10:30</b> ECG 30 minutes	*Rest until imaging Consent completed for drug.	
<b>11:15</b> Lunch	<b>11:00</b> Lunch	<b>1:00</b> FDG PET (fasting for 4 hours) (1.5 hours)	
<b>12:00</b> Clinical Assessment 2 – 3 Hours	*Break until imaging.	<b>2:30 - 3:00</b> Study Drug administration/draw drug specific labs	
	Imaging – starting at Noon <b>12:30</b> AV-45 <b>2:00</b> PET PIB 3 hours		

**13. Are we able to have weekend treatments?**

Yes we have arranged to have the visiting nurses to visit you on weekends if necessary. We will work to make the visits as convenient as possible.



**14. How long would a person be in a trial?**

Initially 2 years. Then the person would either continue on or change drugs depending on how the first drug is evaluated to work.

If one trial is successful, it will continue while enrolling a total of 240 participants. If none of the three original trials is successful, and three new drugs are suitable and available, start 3 new biomarker trials.

**15. If you know you have the mutation, would you be able to tell if the drug is working?**

The drug trial is assessing the change, if any, in biomarkers of participants. The changes may be so small you may not be able to notice them. It is not known for certain what if any changes will be identified.

**16. Will the participant continue taking their current medications (Namenda, Aricept, etc.) while on the trial drug?**

Yes, but we ask that the dose does not change. You would discuss this with the study nurse.

**17. When will the trials begin?**

The trials are beginning at various DIAN performance or partner sites. The first site that is recruiting participants is Washington University but many various sites will begin soon. Individuals who have expressed interest through the Expanded Registry and/or Clinical Trials.gov will be called. We anticipate that the study will have completed enrollment in 12 to 18 months.

**18. Do I have to participate at my own DIAN site?**

It would be ideal for you to go to the DIAN site that knows you well but potentially you could enroll in any DIAN site, if there was a need to.

**19. Can you tell me about the other sites?**

The number of DIAN trial sites is estimated to be approximately 15 in the US with additional international sites.

**Additional Questions**