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DIANTU001: Phase II/III randomized, double-blind placebo in Alzheimer's

Submission date	Recruitment status	[ ] Prospectively registered
25/02/2014	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
25/02/2014	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
16/06/2016	Mental and Behavioural Disorders	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Alzheimer's disease is the most common type of dementia, affecting multiple brain functions including memory. This is a study of two drugs (gantenerumab and solanezumab) in patients who are either known to have a mutation causing Alzheimer's disease, or who don't know their gene status but are "at risk" for an autosomal dominant Alzheimer's disease (ADAD) mutation. The aim is to test whether one or both of these drugs prevent, delay or reverse the changes in the brain that are associated with disease symptoms in ADAD.

Who can participate?
People who are at risk of developing ADAD, aged 18-80 (and between 15 years younger to 10 years older than the age of symptom onset in their affected parent), and who are either symptom free or have mild symptoms of dementia.

What does the study involve?
Participants are randomly allocated to either the gantenerumab or solanezumab group. In the gantenerumab group, participants who are mutation carriers receive either gantenerumab or a placebo (dummy) drug by injection under the skin every 4 weeks. In the solanezumab group, participants who are mutation carriers receive either solanezumab or placebo by injection into a vein every 4 weeks. All mutation non-carriers are allocated to take the placebo. The safety and tolerability of gantenerumab and solanezumab are measured throughout the study period.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
January 2014 to August 2016

Who is funding the study?
1. Avid Radio Pharmaceuticals

2. Eli Lilly and Company Limited
3. Hoffman LaRoche
4. NIH (USA)
5. The Alzheimer's Association

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
15734

Study information

Scientific Title
A Phase II/III randomized, double-blind, placebo-controlled multi-center study of two potential disease modifying therapies in individuals at risk of and with dominantly inherited Alzheimers disease

Acronym
DIANTU001

Study objectives
This is a study of two potential disease modifying therapies (Gantenerumab and Solanezumab) in subjects who are either known to have a mutation causing Alzheimer’s disease OR who don’t know their gene status but are “at risk” for an autosomal dominant Alzheimer’s disease (ADAD) mutation. The purpose is to test whether one or both of these drugs prevent, delay or reverse the changes in the brain that are associated with the development of disease symptoms in ADAD.

Ethics approval required
Old ethics approval format

Ethics approval(s)
13/SC/0535

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: DeNDRoN; Subtopic: Dementia; Disease: Dementia

Interventions
Participants will be randomised 1:1 to either the gantenerumab or solanezumab arm of the study. Within each treatment arm, subjects who are mutation carriers will be randomised to active treatment or placebo at a 3:1 ratio. All mutation non-carriers will be randomised to placebo.

Gantenerumab arm: Subjects will receive either gantenerumab or placebo via injection under the skin every 4 weeks. Solanezumab arm: Subjects will receive either solanezumab or placebo via injection of the drug into the patients vein every 4 weeks.

Adverse events and serious adverse events will be reported by the investigator to the study sponsor and to regulatory bodies as required. Unblinded data on safety-related endpoints and SAEs will be reviewed quarterly by the Data Safety Monitoring Board (DSMB). Amyloid related imaging abnormalities (ARIA), which include cerebral vasogenic oedema and microhaemorrhages, are a safety endpoint. MRI scans will be analysed for ARIA changes at the Mayo clinic.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Gantenerumab, solanezumab

Primary outcome(s)
Safety and tolerability of gantenerumab and solanezumab measured throughout the study period (104) weeks

Key secondary outcome(s)
Not provided at time of registration

Completion date
11/08/2016

Eligibility

Key inclusion criteria
A subject may be included if the answer to all of the following statements is yes:
1. Written consent is signed and dated by the subject, Study Partner (if applicable) and/or by the subjects legally acceptable representative according to local regulations for both the core trial ICF and the drug-specific ICF
2. Subject is 18-80 years of age (inclusive)
3. For women able to have children, the subject must agree to use effective contraceptive measures (e.g., hormonal contraception, intrauterine device, sexual abstinence, barrier method with spermicide) if partner is not sterilised. Men must agree to use effective contraceptive measures
4. Mutation status
4.1. Subject is a carrier 1 of a mutation in PSEN1, APP or PSEN2 gene that is associated with dominantly inherited Alzheimers disease 2 OR at 50% risk for such a mutation (e.g. does not know their mutation status AND is a child or sibling of known mutation carrier)
4.2. Subject is within 15 to +10 years of the age of cognitive symptom onset in the affected parent (refer to Manual of Operations for calculation of estimated age of onset).
4.3. Subjects who are aware that they are mutation negative are not eligible for enrolment.
5. Cognitively normal or with mild cognitive impairment or mild dementia, CDR 01 (inclusive)
6. Fluency in DIAN trial approved language and evidence of adequate pre-morbid intellectual functioning
7. Adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments
8. Receiving stable doses of medication(s) for the treatment of non-excluded medical condition (s) for at least 30 days prior to baseline visit (V2) with the exception of medications taken for episodic conditions (e.g., migraine abortive therapy, antibiotics and other medications for upper respiratory and gastrointestinal ailments), AND, if treated with cholinesterase inhibitors and/or memantine, all of the following conditions are also met:
8.1. The subject has been maintained on a stable dose regimen for at least 90 days prior to screening¿
8.2. The subject is free of any clinically important side effects attributable to the drug.
Side effects that are intermittent, stable or well-tolerated by the subject are not exclusionary.
9. Has a Study Partner who in the investigator's judgment is able to provide accurate information as to the subject's cognitive and functional abilities, who agrees to provide information at the study visits which require study partner input for scale completion, and who signs the necessary consent form if applicable
10. Agrees not to donate blood or blood products for transfusion for the duration of the study and for one year after the final dose of study drug
11. In the opinion of the investigator, the subject will be compliant and have a high probability of completing the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
All

Key exclusion criteria
Subject will be excluded if answer to any of following statements is yes.

CNS Disorder
1. Significant neurologic disease (other than AD) or psychiatric disease that may currently or during the course of study affect cognition or subjects ability to complete study.
2. At high risk for suicide.
Current stable mild depression or current use of antidepressant medications is not exclusionary.
3. History of clinically evident stroke or history of clinically important carotid or vertebrobasilar stenosis, plaque, or other prominent risk factor for stroke or cerebral hemorrhage.
Low dose aspirin (≤ 325 mg daily) is not exclusionary.
4. Alcohol or drug dependence sufficient to meet DSM-IV criteria currently or in past 1 year.
Imaging related exclusion criteria
5. History of or baseline visit brain MRI scan indicative of other significant abnormality
Note: For subjects who have participated in the DIAN observational study, site staff should work with DIAN Observational Imaging Core to review results of MRIs done in the observational study so that those with pre-existing exclusionary findings on MRI are not unnecessarily subjected to screening & baseline visit procedures.
6. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in eyes, skin or body which would preclude MRI scan.

Cardiovascular Disorders
7. Uncontrolled hypertension within 6 months prior to screening
8. Myocardial infarction or other myocardial ischemic events in last 2 years
9. Heart failure resulting in limitation of physical activity
10. History of atrial fibrillation except if only episode which resolved more than three years ago & which treatment
is no longer indicated
11. 12-lead ECG: Clinically significant abnormalities in subjects over 65 years of age.
A discrepancy between local & central read will not be considered a protocol deviation.

Hepatic/Renal Disorders
12. Alanine aminotransferase (ALT) ≥ 2 times the upper limit of normal or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal or baseline total bilirubin ≥ 2 times the upper limit of normal
13. Creatinine clearance lower than 30 mL/min according to Cockcroft-Gault formula (if confirmed at retest)
14. Clinical significant abnormalities in urinalysis.

Infections/Immune Disorders
15. History of Human Immunodeficiency Virus infection, history of Hepatitis B infection within past year, history of Hepatitis C infection which has not been adequately treated or history of spirochete infection of central nervous
system
16. Allergies to humanised monoclonal antibodies or to components of formulations of these antibodies
17. Treatment with immunosuppressive medications within 90 days prior to baseline visit or chemotherapeutic agents for malignancy in last 3 years.

Metabolic/Endocrine Disorders
18. Current clinically significant abnormalities of thyroid function studies, clinically significant deficiency in B12
19. Screening HgbA1C >8% (retesting is permitted if slightly elevated) or poorly controlled insulindependent
diabetes. Subject may be rescreened after 3 months to allow optimisation of diabetic control
20. Morbid obesity with significant comorbidities or would preclude MRI imaging.

Co-Medications
21. Anticoagulants except low dose (≤ 325 mg) aspirin
22. Have been exposed to monoclonal antibody targeting beta amyloid peptide in past six months
23. Received any other investigational treatment within 3 months of screening or 5 half-lives whichever is longer
24. Ever participated in study of an active vaccine or other long-acting biological agent which was being evaluated to prevent or postpone cognitive decline¿

Note: use of approved treatment for AD & other medications is permitted in this study in accordance with Concomitant Medications guidelines (Section 5.3 protocol).

Other:
25. Lack of sufficient venous access
26. Clinically relevant abnormalities in hematology, coagulation studies or clinical chemistry
27. History of cancer in last 5 years, except basal cell carcinoma, non-squamous skin carcinoma, prostate cancer or carcinoma in situ with no significant progression over past 2 years
28. Any other medical condition that could be expected to progress, recur, or change to such an extent that it could bias assessment of clinical or mental status of the subject to a significant degree or put the subject at special risk
29. Currently, or within last month prior to screening, participated in a clinical trial including a nonpharmacological trial with a key objective of improving cognition
30. Positive urine or serum pregnancy test or plan or desire to become pregnant during the course of trial.

Date of first enrolment
01/01/2014

Date of final enrolment
11/08/2016

Locations

Countries of recruitment
United Kingdom

England

United States of America

Study participating centre
University College London
London
United Kingdom
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Sponsor information

Organisation
Washington University in St Louis (USA)

ROR
https://ror.org/01yc7t268

Funder(s)

Funder type
Industry

Funder Name
Avid Radio Pharmaceuticals

Funder Name
Eli Lilly and Company

Alternative Name(s)
Lilly, Eli Lilly & Company, Eli Lilly & Co., Eli Lilly And Co, Eli Lilly & Co

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Funder Name
National Institutes of Health

Alternative Name(s)
US National Institutes of Health, Institutos Nacionales de la Salud, NIH, USNIH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Funder Name
Alzheimer's Association

Alternative Name(s)
Alzheimer's Disease and Related Disorders Association, Inc., Alzheimer's Disease & Related Disorders Association, Inc., Alzheimer's Disease & Related Disorders Association Inc, AA

Funding Body Type
Government organisation

Funding Body Subtype

Associations and societies (private and public)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No